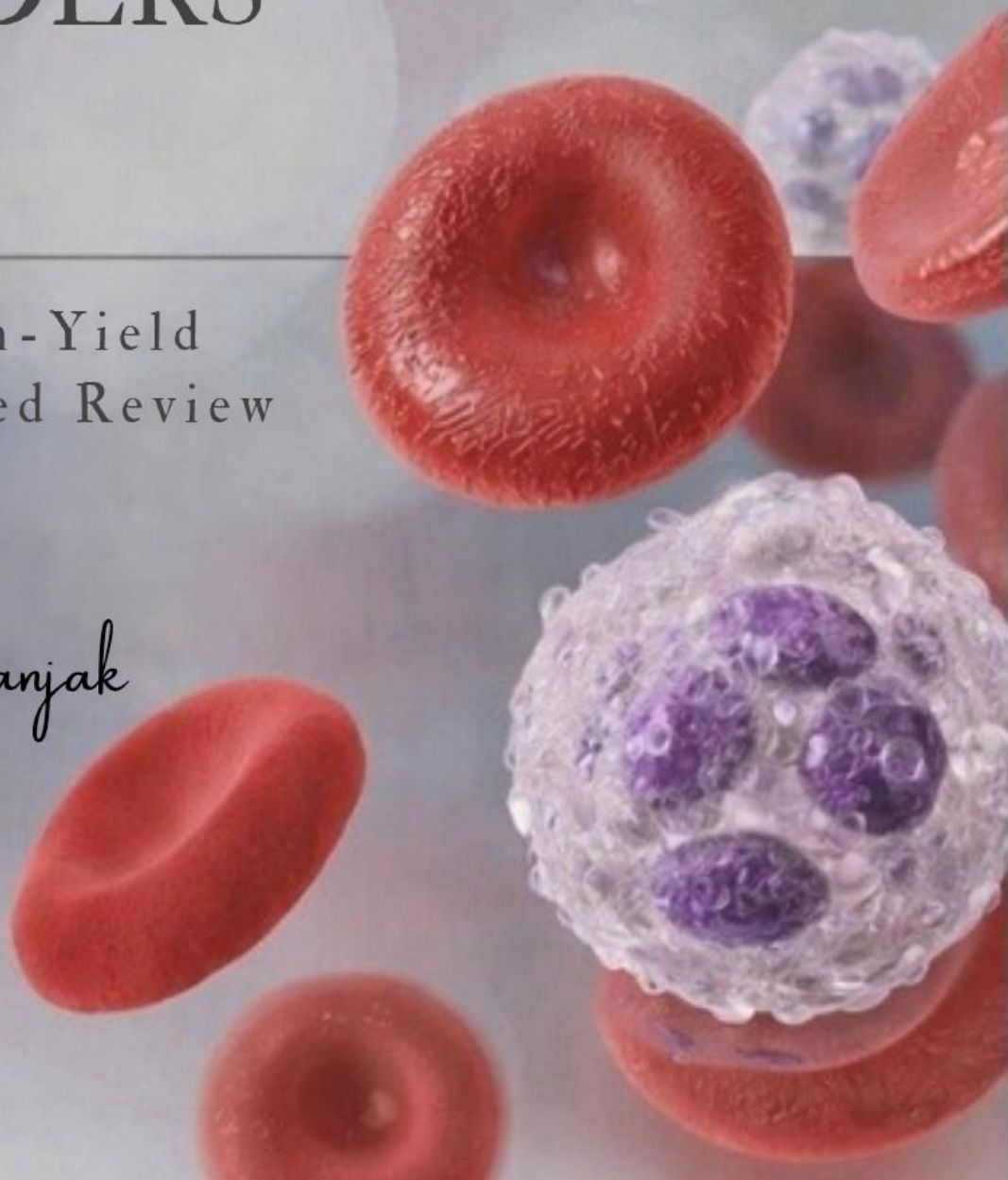
STUDENT TO STUDENT GUIDANCE

RED & WHITE

ERYTHROCYTIC AND LEUKOCYTIC DISORDERS

A High-Yield Illustrated Review



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Disclaimer

This book is intended for educational purposes only.

The information provided is designed to support learning and revision in hematology and should not be used as a substitute for professional medical advice, diagnosis, or treatment.

The content of this book is not intended to guide clinical decision-making or patient management. Readers are advised to consult standard medical textbooks, clinical guidelines, and qualified healthcare professionals for diagnosis and treatment of medical conditions.

The author makes no warranties regarding the completeness or accuracy of the information and assumes no responsibility for any consequences arising from the use or misuse of the material contained in this book.

Preface

This book was written to provide a clear and concise introduction to hematology for medical students and junior trainees. Hematology is often perceived as a complex subject due to the integration of clinical concepts with laboratory findings, and this book aims to simplify these topics while maintaining scientific accuracy.

The content focuses on core principles of hematology, including anemia, hemolytic disorders, bone marrow failure syndromes, and essential laboratory investigations. The material is presented in an exam-oriented and structured manner to facilitate understanding and revision.

This book is intended as a supplementary educational resource and does not replace standard textbooks or clinical guidelines. It is my hope that this work will assist learners in building a solid foundation in hematology and encourage further study of this important field.

Chapter 1 : introduction

Introduction

Hematopoiesis is the dynamic and highly regulated biological process by which **multipotent hematopoietic stem cells** (HSCs) **differentiate**, **proliferate**, and **mature** into all types of blood cells (red blood cells, white blood cells, and platelets). This process begins early in embryonic development and continues throughout life to maintain a balanced supply of blood cells according to the body's physiological needs.

Regulation of hematopoiesis involves a complex network of **soluble factors** (erythropoietin , thrombopoietin, granulocyte colony-stimulating factor and monocyte colony-stimulating factor), **cytokines**, and **cellular interactions** that ensure proper production, renewal, and function of the blood cell lineages.

Hematopoietic stem cells originate primarily from the **yolk sac** and, to a lesser extent, from the mesoderm of the aorta–gonad–mesonephros (AGM) region.

Around the third month of gestation, these cells migrate mainly to the **liver** and **spleen**

Around the fourth month, hematopoiesis shifts to the **bone marrow**, while hepatic hematopoietic activity gradually declines and eventually ceases after birth.

After adulthood Hematopoiesis restrict on the active -red- bone marrow e.g axial skeleton and proximal ends of long bones . The rest of bones (yellow marrow) are not involved in hematopoiesis but red marrow expansion can occur in some situations.

(Remember that, as stem cells change their microenvironment by migration , the cells they produce also undergo some sort of changes , So each of these locations has distinct but still related populations of cells.)

The term **Extramedullary** hematopoiesis stands for the production of blood cells outside the bone marrow . While it is a normal intrauterine phenomenon , abnormal extrauterine extramedullary hematopoiesis can occur as a compensatory mechanism when bone marrow can't meet the physiological demands of the body for example in situation of severe anemia like thalassemia and sickle cell disease

For exam purposes remember just that :

yolk sac derives hematopoiesis during first trimester

Liver and spleen derive hematopoiesis during 2nd trimester

Bone marrow of all bones derive the 3rd trimester hematopoiesis

After puberty hematopoiesis take place in the still active bone marrow (axial bones and proximal ends of long bones)

Chapter 2 : RBCs disorders

Anemia

Disorders of red cells can result in **anemia** or, less commonly, **polycythemia** (an increase in red cells also known as erythrocytosis)

Anemia is a medical condition characterized by a **decrease in the number of circulating red blood cells** (RBCs), a **reduced concentration of hemoglobin** (Hb), or a **lower hematocrit** (packed cell volume) than normal, resulting in inadequate oxygen delivery to the body's tissues.

WHO defines anemia as a hemoglobin values below approximately 13 g/dL in adult men and below 12 g/dL in nonpregnant adult women

Anemia can stem from **bleeding**, **increased red cell destruction**, or **decreased red cell production**

Clinical feature of anemia :

-Symptoms of anemia depend on the rapidity of onset and severity.

-Chronic anemia may be asymptomatic because of a compensatory mechanisms .

-Symptoms are usually non-specific:

fatigue, headache, dizziness, syncope, dyspnea, palpitations , decreased work or intellectual capacity.

-Symptoms of exacerbation of cardiac issues (angina, intermittent claudications)

Patient history is critically important in diagnosis of anemia and may provide key clues; for example:

Anemia + history of chronic NSAID use with black stools is suggestive of anemia due to gastrointestinal bleeding.

Anemia + Vegetarian patient is suggestive for B12 and/or iron deficiency anemia

Anemia + history of chemotherapy or radiation is suggestive for aplastic anemia

Anemia + history of pica (craving non-food substances such as ice, clay, or dirt) is suggestive for iron deficiency anemia

Signs of anemia:

Pallor (due to low hemoglobin in circulation , so less color is delivered to tissues, making them appear pale . Redistribution of the blood away from non-essential superficial capillary beds (like the skin) towards vital organs also contribute in pallor)

Tachycardia (compensatory cardiovascular response to anemia)

Systolic flow murmur (a functional murmur result from increased blood velocity across valves)

Cardiac failure (High-output failure)

Specific signs seen in different types of anemia include:

Koilonychia (spoon-shaped nails) :seen with longstanding iron-deficiency anemia

Jaundice : seen with hemolytic anemia

Bone deformities : seen with thalassemia major

Leg ulcers : seen with sickle cell disease

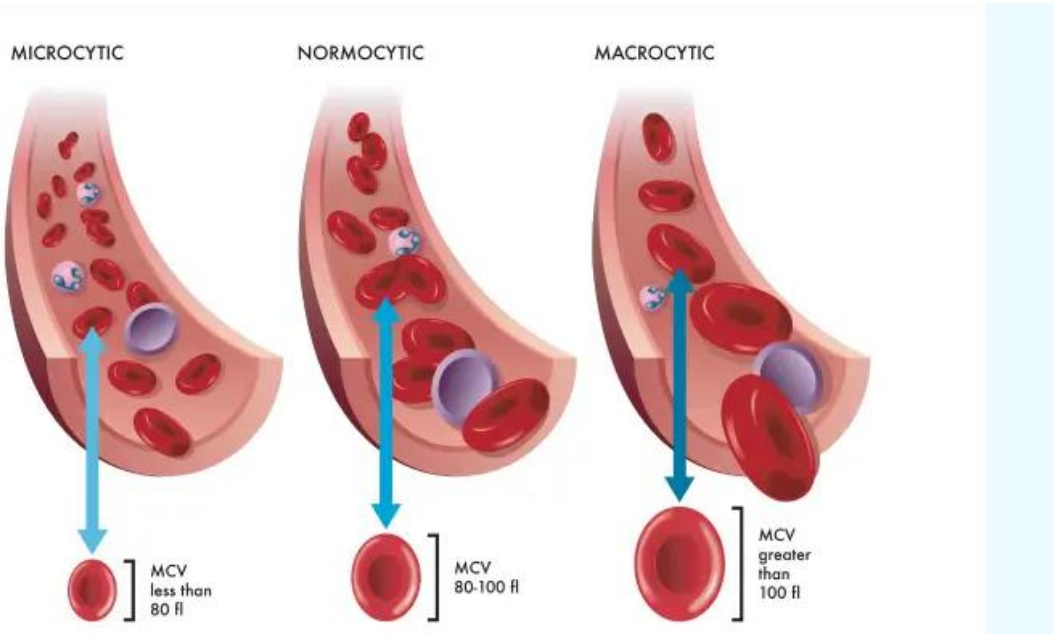
<u>Anemia can be classified according to the underlying mechanism into</u> :

-Anemia of blood loss

-Increased Destruction (Hemolytic Anemias)

-Impaired Red Cell Production

<u>According to morphology classified as normocytic, microcytic or macrocytic</u>



Anemias due to decreased production

Iron deficiency anemia :

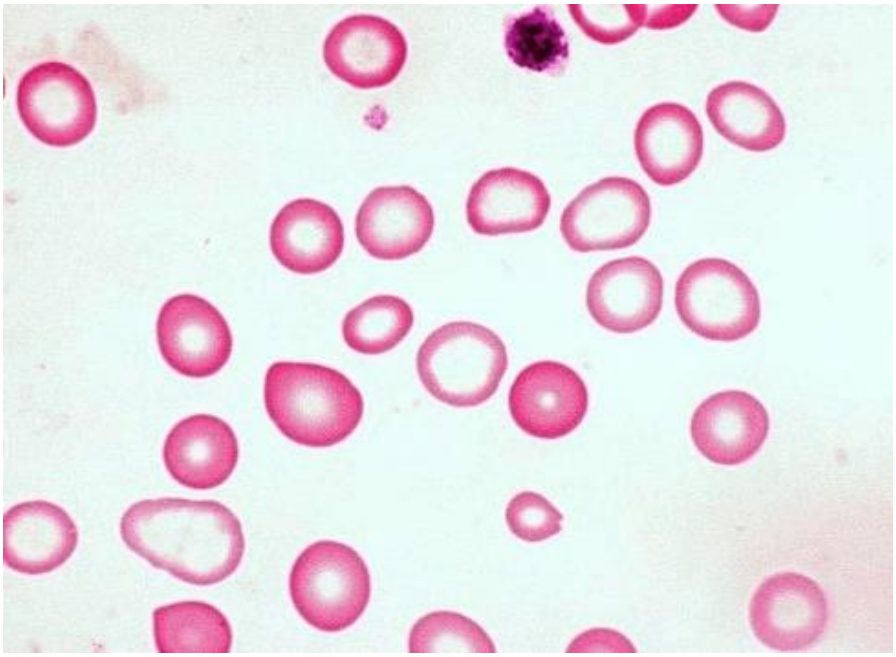
Deficiency of iron is the **most common nutritional deficiency** in the world and results in clinical signs and symptoms that are mostly related to anemia.

Iron is an essential component of hemoglobin , therefore iron deficiency negatively impacts hemoglobin synthesis.

Iron deficient RBCs contain less amount of hemoglobin, making them pale (hypochromic). In addition, they are smaller in size because erythroid precursors continue to divide in order to match the cell size to the amount of hemoglobin inside , resulting in microcytosis .

So , iron deficiency characterized by a **hypochromic microcytic anemia .**

(Note :In early stages the RBCs may be normocytic normochromic)



Iron metabolism

Iron is a potentially hazardous substance, and humans (especially males and non-menstruating females) do not possess advanced mechanisms for iron excretion. Therefore, regulation of the amount of iron in the body is achieved through control of iron absorption.

Dietary iron :

Heme - iron (organic iron) from animal sources . Exist in ferrous (Fe^{2+}) state and have better bioavailability and absorption profile

Non - heme iron from plant sources . exists in the ferric (Fe^{3+}) form and must be reduced to the ferrous form before absorption . Its absorption is variable and is influenced by dietary enhancers such as vitamin C and inhibitors such as tannate (in tea), and oxalate (in spinach)

Iron absorption occurs mainly in the **duodenum** and **upper jejunum**. heme iron is absorbed directly, while non-heme iron is reduced from Fe^{3+} to Fe^{2+} before uptake by **divalent metallic transporter 1** (DMT1). Now inside enterocytes iron can either stored as **ferritin** (for later use or to be lost when enterocytes are naturally shed) or exported via ferroportin into blood, where it binds **transferrin** to be transported to bone marrow and tissues where it used and also stored as ferritin .

The fraction of iron that is absorbed is regulated by **hepcidin**, a small peptide that is synthesized and secreted from the liver. Hepcidin negatively impact iron absorption from gut by binding and inactivation of ferroportin . Hepcidin levels are increased by high iron stores and inflammation and decreased by iron deficiency, hypoxia, and increased erythropoietic demand.

(Note that : Most of the body's iron comes from recycling of senescent red blood cells by macrophages in the spleen, liver, and bone marrow, which release iron back into circulation via ferroportin)

Important laboratory measurements to detect iron statues:

Serum iron : measures the amount of iron circulating bound to transferrin; decreased in iron deficiency

Total iron binding capacity (TIBC) : reflects the total transferrin available to bind iron; increased in iron deficiency (when iron is deficient there is more available empty sites o2n transferrin)

Transferrin saturation : In normal persons, transferrin is about 33% saturated with iron; if the saturation is low that suggests iron deficiency

Serum ferritin : reflect storage status , it is a good measure of iron stores ; low serum ferritin is suggestive for iron deficiency

(Note : Assessment of bone marrow iron is another reliable but more invasive method for estimating iron stores)

Etiology of iron deficiency

Iron deficiency can result from :

- **Reduced iron intake** : Vegetarian and vegan diets , poor diet, breast milk (infants especially preterm or low-birth-weight are prone to iron deficiency because of low content of iron in breast milk)
- **Reduced absorption** : celiac disease , atrophic gastritis , gastrectomy (HCl help reduction of ferric to ferrous) , dietary inhibitors of iron absorption such as phenols and phytates , some medications like tetracycline and PPI also can affect iron absorption
- (Note that : gastrectomy also can cause B12 deficiency "see later" , so patient with gastrectomy and a wide RDW you should consider double deficiency anemia)
- **Increased demand :** like pregnancy **,** growth spurts

- **Chronic blood loss : Menstrual bleeding** (menorrhagia), GI bleeding (**peptic ulcer**, polyps, colorectal cancer, hemorroids or less commonly angiodysplasia) , **parasitic infection** , frequent blood donation
- **Other Contributing causes :** chronic disease/inflammation (reduce iron mobilization from storages) , chronic hematuria or bleeding diatheses, genetics

In the developing world, low intake and poor bioavailability because of predominantly vegetarian diets are the most common causes of iron deficiency .

Chronic blood loss is the most important cause of iron deficiency anemia in the Western world .

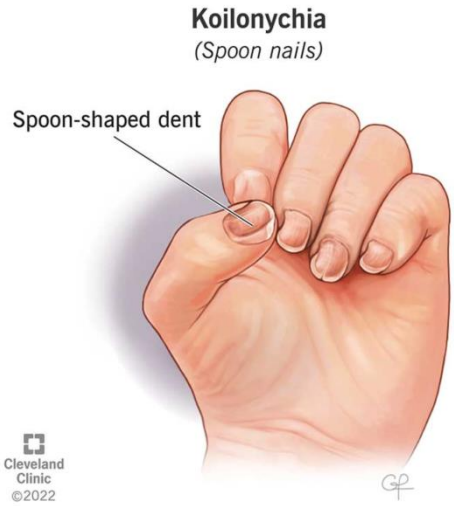
Clinical feature

- Signs and symptoms related to anemia (dizziness, palpitations, dyspnea)
- Signs and symptoms related to underlying cause (e.g GI bleeding, gynecological issues)

Special features :

- **Pica** (craving and compulsive ingestion of nonnutritive substances such as ice, soil, or clay)
- Nail fragility and **koilonychia**
- **cheilosis**, **atrophic glossitis**
- Hair loss
- dysphagia caused by formation of esophageal webs (Plummer-Vinson syndrome)

angular stomatitis



Management:

Investigate and treat the underlying cause (e.g. endoscopy to identify gastrointestinal bleeding).

Iron replacement: ferrous sulfate 200 mg three times daily (tds) for adults, or 9 mg/kg once daily (od) for children from 6 years of age . IV iron should be considered in some situations

Reassessment:

expect Hb rise of 1–3 g/dL after 3–4 weeks.

Lack of response suggests:

Non-compliance.

Ongoing blood loss.

Incorrect diagnosis.

Continue iron therapy for 3 months after normalization of Hb to replenish iron stores

Anemia of chronic diseases/inflammation

Anemia of chronic inflammation (also called anemia of chronic disease) is a common type of anemia that develops in people with long-standing illnesses such as chronic infections, autoimmune diseases, cancer, or other conditions that cause ongoing inflammation. In these situations, inflammatory cytokines (especially interleukin-6) stimulate the liver to increase production of the hormone hepcidin, which blocks iron release from storage cells and reduces iron absorption from the gut, leading to reduced iron availability for red blood cell production even though total body iron stores are usually normal or high.

Laboratory findings

Decreased serum iron (low available iron)

Increased ferritin (reflect increased iron stores)

Decreased TIBC

normocytic normochromic anemia in early stages

Microcytic hypochromic anemia in late stages (marked functional iron deficiency)

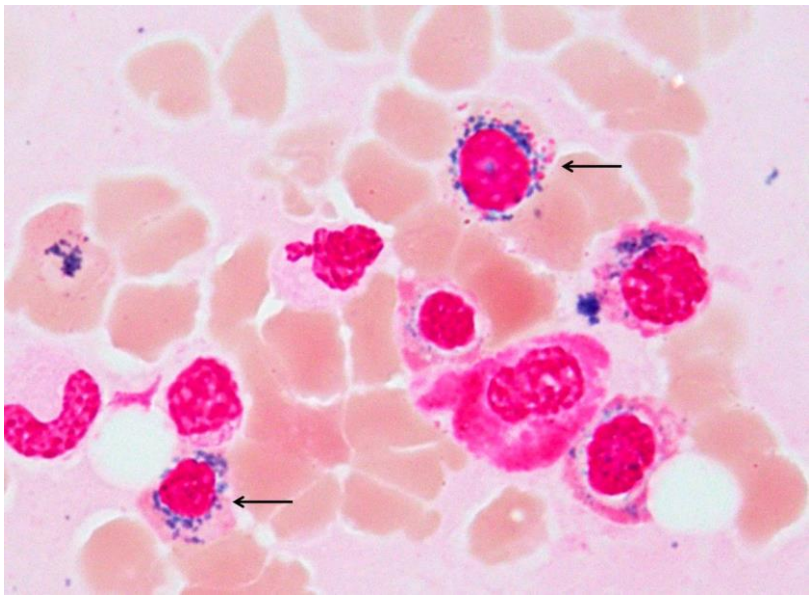
Management

Supportive

Treat the underlying cause

An overview to sideroblastic anemias

Sideroblastic anaemias (SA) are a group of disorders characterized by the presence of **ring sideroblasts** in the bone marrow. Sideroblasts are erythroblasts with excess iron accumulated in their mitochondria, forming a ring around the nucleus.



Sideroblastic anaemias are classified into inherited (congenital) and acquired forms.

The inherited forms are caused by well-defined mutations in nuclear or mitochondrial DNA. These mutations affect the heme synthesis pathway especially **ALA synthase**

The acquired forms are more common. They may be reversible when caused by drugs , nutritional deficiencies i.e **B6 deficiency,** or environmental exposure i.e **lead poisoning** .In other cases, sideroblastic anemia occurs as part of a clonal bone marrow disorder, especially **myelodysplastic syndrome** (MDS). In these cases, the acquired mutations responsible for the sideroblastic phenotype are largely unknown.

In heme synthetic pathway there are two important enzymes:

ALA synthase, which requires vitamin B6 as a cofactor

ferrochelatase which is last step in heme synthesis in which the iron is incorporated to protoporphyrin ring , here the lead competing with iron and preventing its incorporation into protoporphyrin

Laboratory findings

Increased ferritin

Increased serum iron

Decreased TIBC

Microcytic hypochromic RBCs in blood picture

sideroblasts in bone marrow biopsy or aspiration

Management outlines

- **Manage the underlying cause :** stop the causative drug , mange lead poisoning, deal with alcohol abuse, correct B6 deficiency
- For many patients especially those with X-linked or acquired forms a trial of pyridoxine (vitamin B6, typically 50–100 mg/day) is recommended, as it can partially or completely correct anemia in responsive cases

- **Blood transfusions** are used for severe or symptomatic anemia that does not respond to B6
- **Manage the complications** i.e iron overload

Always remember, in practice, a primary care doctor or general internist can start initial work-up and supportive care, but **referral to a hematologist** is recommended for confirmation of diagnosis, tailored therapy, specialist treatments (e.g BM transplant and novel drugs) , and long-term follow-up.

B12 & Folic acid deficiency anemias

The terms **Megaloblastic\Macrocytic** anemia are usually used interchangeably to describe that type of anemia caused by either B12 or folic acid deficiency . But scientifically there is a core difference between the two terms :

- Megaloblastic anemia describe the presence large erythroblasts with delayed nuclear maturation in the bone marrow because of defective DNA synthesis (i.e B12/folic acid deficiency)
- Macrocytosis describe the presence of increased MCV (>100 fl) in peripheral blood , and it is not necessarily accompanied by presence of megaloblasts in bone marrow (reticulocytosis as an example)

both B12 and folic acid deficiencies have an identical hematological feature (megaloblastic anemia) , in addition B12 have a unique neurological disturbances (**subacute combined degeneration**) see later . (Note that : Folic acid deficiency during peri-conceptional period is strongly linked to neural tube defects i.e spina bifida and anencephaly)

The impaired of DNA synthesis affects the neutrophils leading to nuclear hypersegmentation and reduction in total number of neutrophils. Also other rapidly dividing cells and platelets are affected so the term megaloblastic pancytopenia is more acute

Most of morphologically abnormal RBCs precursors are hemolyzed inside bone marrow (intra medullary hemolysis) , so you may found slight evidence of hemolysis i.e increased LDH and indirect bilirubin

Pathophysiology

Without diving deeply into details we can simply say that :

-Folic acid is essential for nucleotides (the building blocks of nucleic acids) synthesis specifically the synthesis of thymidine . So folate deficiency result in defective DNA synthesis and subsequently megaloblastosis

-B12 is essential for normal folic acid function and deficiency of it resulting in a physiological deficiency of folic acid.

-B12 is also an essential cofactor in enzymatic conversion of :

- **Homocysteine** to **methionine**
- **Malonyl-CoA** to **Succenyl-CoA**

So B12 Deficiency cause :

- Increased homocysteine (homocysteinemia) which is associated with increased risk of atherosclerosis
- Decreased methionine which inturn results in decreased choline containing phospholipids which are necessary for nerve myelination
- Increased Malonyl-CoA and its upstream substrate propionyl-Coa which are integrated to and disrupt the integrity of myelin sheath.

Notes :

increased **methylmalonic** acid is a sensitive indicator for B12 deficiency

Folic acid deficiency is also associated with homocysteinemia but not increased methylmalonate .

Dietary background:

Folic acid is present in food such as green vegetables, fruits, meat, and liver. Folic acid is mainly absorbed in the jejunum and the body stores around 5 mg of folate in the liver, which is enough for 3 to 4 months

The primary dietary sources of cobalamin/vitamin B12 are meats, fish, eggs, and dairy products. Vegan diets are low in vitamin B12. However, not all patients following a vegan diet develop clinical evidence of deficiency. Vitamin B12 is first bound within the duodenum and jejunum to the **intrinsic factor** (IF) produced by gastric parietal cells and is then absorbed in the **terminal ileum**. The body stores 2 to 3 mg of vitamin B12 in the liver (sufficient for 2 to 4 years)

Note that : the dietary b12 is tightly coupled with animal proteins , in the stomach HCl and pepsin degrade this proteins to release b12 . Then b12 is rapidly being trapped by cobalophillins (Rapid binders) . In the duodenum and jejunum pancreatic enzymes freeing b12 to be coupled with intrinsic factor (produced by gastric parietal cells) which help its absorption.

B12 deficiency :

Etiology:

-Reduced intake: rare and requires many years of strict vegan diet

-Decreased absorption: pernicious anemia (the most common cause) , post gastrectomy , atrophic gastritis , conditions affecting ileum (Ileal resection , Crohn's disease, TB) , certain drugs interfere with B12 absorption (Metformin) , Pancreatitis, parasitic infection by diphyllobothrium latum , and bacterial overgrowth

Pernicious anemia

Pernicious anemia is a megaloblastic anemia due to B12 deficiency which is due to **intrinsic factor deficiency** that **stem from autoimmune destruction** of gastric partial cells

Usually associated with other autoimmune diseases, particularly thyroid disease, Addison's disease, and vitiligo

histologically, there is a chronic atrophic gastritis marked by a loss of parietal cells, a prominent infiltrate of lymphocytes and plasma cells, and megaloblastic changes in mucosal cells similar to those found in erythroid precursors.

The serum of most affected patients contains several types of autoantibodies that block the binding of vitamin B12 to intrinsic factor or prevent binding of the intrinsic factor–vitamin B12 complex to cubilin.

Autoantibodies are of diagnostic use, but they are not thought to be the primary cause of the gastric pathology , in fact antibodies are produced secondary to T-cell mediated destruction and release of the contents of partial cells

Clinical features

-Symptoms and signs of anemia

-Glossitis (**beefy-red** sore tongue)

-Lemon tinge to skin due combination of pallor (anemia) and mild jaundice (due to hemolysis)

- In sever cases you may found signs and symptoms of decreased platelets and neutrophils

The neurological symptoms include:

- Paresthesias-most often in fingers and toes (the most common symptom of vitamin B12 Deficiency) .
- Dorsal column modality sensation loss (diminished vibratory sense and sensory ataxia)
- Abnormal deep tendon reflexes
- Memory loss
- Personality change
- Orthostatic hypotension

patients can have neurological damage due to B12 deficiency without anemia. In fact as many as 30% of patients with neurological disease due to B12 deficiency will have no or only subtle hematological symptoms.

laboratory findings

-Decreased B12

-Increased homocysteine

-Increased malonylate

-Oval **macrocytosis** with **hypersegmented** neutrophils

-Megaloblastosis in bone marrow aspiration or biopsy

Management

replace the deficient vitamin : vitamin B12 supplements, either by injections or high-dose oral tablets, depending on the cause . B12 injections (1000 mcg intramuscularly) are usually given initially (often weekly for a few weeks) and then continued monthly . If the deficiency is due to a dietary lack and absorption is normal, high-dose oral B12 may be effective

treating the underlying cause : e,g hookworm infection, Crohn's disease

Folic acid deficiency

Etiology

-Decreased intake

-Increased requirements : pregnancy , hemolytic anemias , malignancies (increased needs for folate result in rapidly development of folate deficiency if intake is not kept up) .

-Malabsorption

-Drugs : Patient with underlying mild folate deficiency are more susceptible to trimethoprim/sulfa, pyrimethamine and methotrexate toxicity. Oral contraceptive and anticonvulsants lead to increase consumption of folate.

-Alcohol : affects several aspects of folate metabolism. **Alcoholics have poor intake of folate**. Also interfere with folate metabolism leading to a functional folate deficiency.

Clinical features

Similar to B12 deficiency except in neurological manifestations

Laboratory findings

-Decreased folic acid (measuring RBCs folic acid is preferred)

-Increased homocysteine

-Unlike b12 deficiency malonylate not affected

-**Oval macrocytosis** with **hypersegmented neutrophils**

-Megaloblastosis in bone marrow aspiration or biopsy

-FIGLU (N-formimino glutamate) in urine

Management

-Replacement of folic acid: 1 mg daily for 4 months or until blood counts normalize.

-Deal with the underlying cause

Never give high dose of folic acid until B12 deficiency is ruled out or treated to avoid iatrogenic exacerbation of neurological disorders because:

- Supplementation with folic acid exacerbate B12 deficiency (rapid consumption of B12)
- Folic acid can improve the blood picture in B12 deficiency without treating the nerve damage , so its treat hematological problems and mask the the true deficiency with ongoing neurological damage

Note : Pregnant women given 400–800 µg folic acid daily before and during pregnancy to prevent deficiency and neural tube defects.

Aplastic anemia

Aplastic anemia is defined **as pancytopenia** with **hypocellularity** (aplasia) of the bone marrow. The term aplastic anemia can lead to misunderstanding; there is also thrombocytopenia and granulopenia There is no abnormal cells in bone marrow or peripheral circulation.

It is usually an acquired condition but may rarely be inherited.

The problem stem from destruction or reduced proliferative capacity of myeloid stem cells in bone marrow .

Note that : the type of anemia which result from bone marrow infiltration is called **myelophthisic anemia**

Etiology

- Radiation
- Chemicals
- Drugs , either as dose dependant fashion (occurs in all recipient) or as idiosyncratic reaction (unpredictable reaction in vulnerable individuals)
- Infections (transient, mild blood count depression is frequent in the course of many viral and bacterial infections . Parvovirus B19 is a cause of pure red cell aplasia and rarely implicated in generalized bone marrow failure) .
- Immunologic Diseases
- Hepatitis (non-A, non-B, non-C post-hepatitis marrow failure . is presumed to be immune-mediated)
- Pregnancy (very rare complication of pregnancy)
- Paroxysmal Nocturnal Hemoglobinuria
- Fanconi anemia (defective DNA repair mechanics, hypoproliferative myeloid stem cells , multiple physical abnormalities and increased risks to many cancers)

Clinical features

-Signs and symptoms of anemia

-Signs and symptoms of low platelet count (e,g easy bruising , petechiae and bleeding gums)

-Sings and symptoms of low granulocytes (recurrent infections)

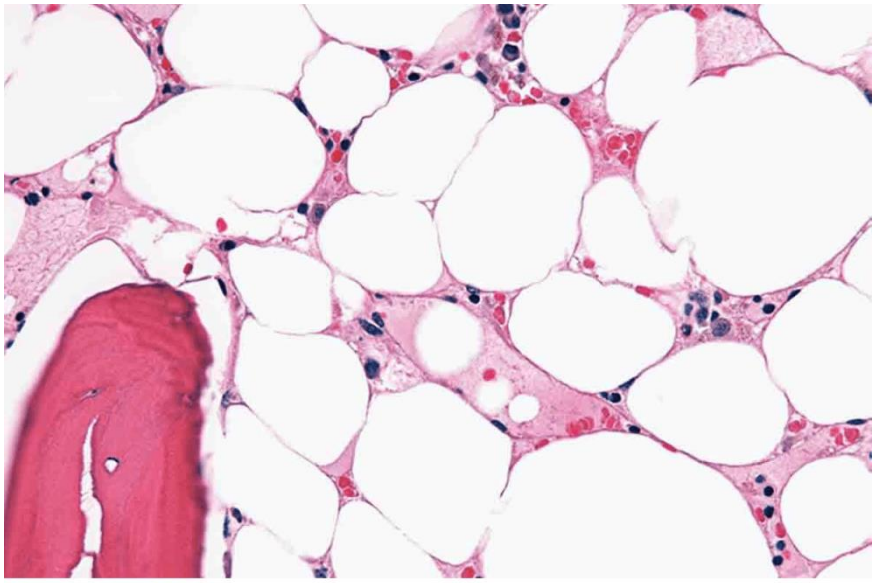
laboratory findings

-Low RBCs count

-Low platelet count

-Low granulocytes count

-Hypocellular -empty- marrow on bone marrow examination



Hypocellular -empty- marrow

Management

-**Supportive care** : treat infections, blood transfusions , growth factors (e.g G-CSF/filgrastim), avoid contact

-**Immunosuppressive therapy** can improve bone marrow function in many patients.

-**Stem cell transplant**

Hemolytic anemias

Hemolytic anemias (HAs) are a diverse group of disorders that have as a common feature **accelerated red cell destruction** (hemolysis).

Healthy bone marrow capable to compensate up to five times increase in destruction rate . If the rate of destruction overwhelms bone marrow compensation or there is associated haematinic deficiency the patient will develop anemia .

If bone marrow compensation not exceeded this condition is called **compensated hemolytic disease** .

Hemolytic anemias can be classified as :

intrinsic (intracorpuscular) Vs **extrinsic** (extracorpuscular) : basically this classification based on whether the cause of hemolysis is intrinsic abnormality in RBCs e.g enzyme deficiency or extrinsic outside RBCs e.g mechanical trauma to red cells such as in prosthetic heart valves for example

extravascular Vs intravascular : more clinically useful approach groups hemolytic anemias according to whether hemolysis is primarily extravascular (macrophages of RES) or intravascular (inside blood vessels) .

Extravascular hemolysis is caused by defects that increase the destruction of red cells by phagocytes, particularly in the **spleen.**

Intravascular hemolysis, by contrast, is characterized by injuries so severe that red cells literally burst within the circulation

Physiological review of normal RBCs destruction :

- the life span of RBCs is about 120 day
- Senile RBCs cleared and degraded by macrophages of RES .
- The lipid , protein and ions -particularly iron- components of RBCs are reutilized again , while protoporphyrin metabolized to bilirubin for further excretion.
- In blood bilirubin is bound mainly to albumin and transferred to the liver to be conjugated with glucurinate and then excreted with bile
- Then bilirubin metabolized by colonic bacteria to urobilinogen , then:
- Urobilinogen excreted with faeces as stercobilin which give the characteristic colour of the stool
- Urobilinogen also absorbed again by enterohepatic circulation to the liver which inturn excrete it again

- Only small fracture of urobilinogen leaks to systemic circulation and excreted by kidneys (but does not stain urine , the colour of urine is determined by urochrome)

From this rapid review you can expect the followings in hemolysis :

-Increased unconjugated bilirubin

-Dark stool

-Increased urobilinogen in urine

Evidence of hemolysis :

- Compensatory increased RBCs production :
- reticulocytosis and it's consequences (i.e slight increase in MCV and polychromasia)
- erythroid hyperplasia of bone marrow
- Increased RBCs destruction:
- Anemia
- Increased unconjugated/indirect bilirubin (if exceed 2.4 mg/dl will be accompanied by jaundice)
- Increased LDH (from destructed cells)
- Decreased haptoglobin (haptoglobin is a glycoprotein produced by the liver and it's function is to binding free hemoglobin in the blood to prevent loss hemoglobin in urine)
- Hemoglobinemia and hemoglobinuria (which cause dark urine) are signs of intravascular hemolysis. Methemoglobinemia can also be present. Hemosiderin in the urine (hemosiderinuria) indicates chronic intravascular hemolysis.
- +ve Schumm's test (intravascular hemolysis)
- Splenomegaly due to work load hyperplasia on spleen (extravascular hemolysis)
- Morphological abnormalities in RBCs may be found in blood film (e.g schistocytes , heinz body, target cell and others)
- Bilirubin stone (most likely chronic extravascular hemolysis)
- Acute tubular necrosis (massive intravascular hemolysis , due to toxic effect of free hemoglobin on renal tubular cells)

Intracorpuscular hemolytic anemias:

The problem causing the premature destruction of RBCs lies within the RBCs themselves .

Commom causes :

-Inherited:

- Membranopathies : hereditary spherocytosis and hereditary elliptocytosis
- Hemoglobinopathies: sickle cell anemia and unstable hemoglobins
- Deficient hemoglobin synthesis: thalassemia syndromes
- Enzymopathies :Glucose 6 Phosphate dehydrogenase , glutathione synthase, pyruvate kinase, hexokinase deficiency

-Acquired :

- Paroxysmal nocturnal hemoglobinuria

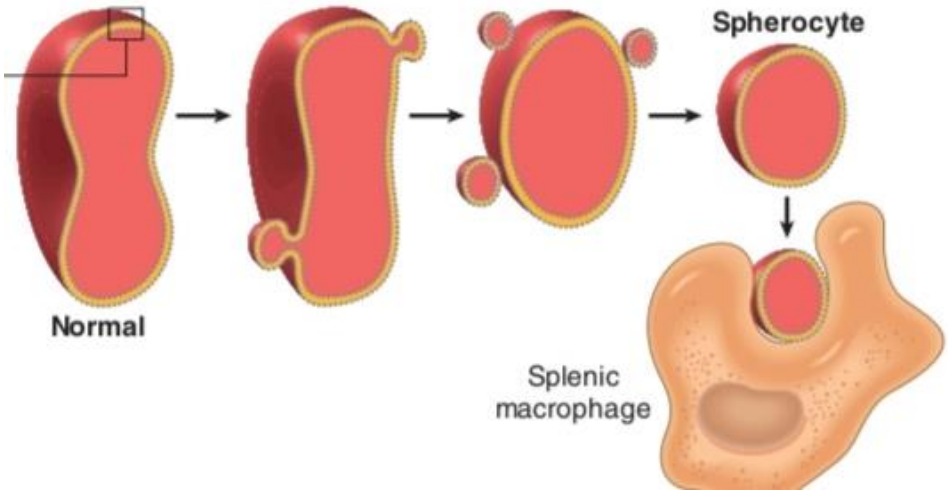
Hereditary spherocytosis :

Hereditary spherocytosis is the most common form of inherited hemolytic anemias (G6PD deficiency is the most common enzyme defect world wide but in most of patients the severity not enough to cause anemia and most patients are asymptomatic)

This disorder stems from inherited (intrinsic) defects in the red cell membrane that lead to the formation of **spherocytes**, nondeformable cells that are highly vulnerable to sequestration and destruction in the spleen

Usually inherited as autosomal dominant fashion , and a small minority as a more severe autosomal recessive version.

Hereditary spherocytosis is caused by inherited defects in membrane skeleton proteins (e.g. **ankyrin**,**spectrin**, **band 3**, protein 4.2) that stabilize the red cell lipid bilayer, leading to membrane instability with progressive **loss of membrane** through vesicle shedding, a reduced surface area-to-volume ratio, and formation of spherocytes that are prone to splenic destruction.



Notes:

Spherocytosis may be acquired , and any acquired cause of partial membrane loss can cause acquired spherocytosis and its most commonly associated with **autoimmune hemolytic anemias**.

Elliptocytosis resembles hereditary spherocytosis; however, membrane loss is minimal, and red cells become elliptical not spherical.

Clinical features:

The main clinical findings are jaundice, splenomegaly, and often **gallstones** (The presence of pigmented gallstones in a young adult should raise suspicion for hereditary spherocytosis , also other causes of chronic extravascular hemolytic anemias can cause it)

HS shows a wide range of clinical severity, from severe infantile anemia to mild disease presenting in adulthood.

the most important differential diagnosis is **autoimmune hemolytic anemia**, which can usually be excluded by a negative direct antiglobulin test (DAT) result

Note that there is an increased risk for aplastic crisis with parvovirus B19 infection of erythroid precursors.

Laboratory findings :

Usually normocytic spherocytes

increased MCHC >34 g/dL (hyperchromic with loss of central pallor that is normally found)

+Ve **osmotic fragility test** (increased fragility of RBCs in hypotonic solution because of spherocytosis can't accommodate osmotic swelling)

Management:

-Observation and Supportive Care : Most patients require no specific treatment , folic acid supplementation to support erythropoiesis , blood transfusion if needed (Rarely, patients are transfusion-dependent) and regular monitoring

-Splenectomy: definitive symptomatic treatment(current recommendations are to perform splenectomy between 4 and 6 years of age in severe cases, to delay splenectomy until puberty in moderate cases, and to avoid splenectomy in mild disease)

-Management of complications : Aplastic crisis, gallstones

Notes :

-Spleen have a vital role in the immunity against encapsulated bacteria (**S.pneumoniae** , H.influenzae , N.meningiditis and salmonella) so prophylatic antibiotics and vaccination is important to be considered ;splenectomy should be preceded by appropriate immunization and followed by life-long penicillin prophylaxis

-After splenectomy anemia is improved, but spherocytosis persists and there are leukocytosis ,thrombocytosis, reticulocytosis and **Howell-Jolly bodies** are found in blood tests

-Howell-Jolly bodies are basophilic nuclear remnants in erythrocytes indicating **hyposplenism** or **post-splenectomy** state (normally spleen destroys defected RBCs , presence of Howell–Jolly bodies indicates failure of splenic removal) .

Sickle cell disease/anemia:

Sickle cell anemia is a genetic blood disorder where red blood cells become rigid and sticky and are shaped like sickles or crescents.

Is the most common familial hemolytic anemia, with a high gene frequency in malaria-endemic regions ,reflecting a selective survival advantage against Plasmodium falciparum malaria.

In Sudan, sickle cell disease is concentrated in the western regions and is strongly associated with particular ethnic groups such as the **Messeryia**, Hausa, Massaleet , Baggara, Fur, and other populations with substantial African ancestry. Among Sudanese ethnic groups, the Messeryia tribe of western Sudan (Darfur and Kordofan) shows the highest burden of sickle cell disease, with an estimated risk of approximately 1 in every 123 children being born with sickle cell disease.

SCA caused by **a point mutation** in β-globin that creates sickle hemoglobin (HbS).

When an individual is heterozygous (one defective β-globin gene from one parent) it's called sickle cell trait rather than anemia because sufficient normal hemoglobin (HbA) is produced to prevent chronic hemolysis and anemia.

SCA is caused by a single amino acid substitution in β-globin that results in a tendency for deoxygenated HbS to self-associate into polymers (which distort the red blood cell membrane and alter its shape and flexibility and become rigid and take up their characteristic sickle appearance)

Sickling is precipitated by infection, dehydration, cold, stress, acidosis, and hypoxia.

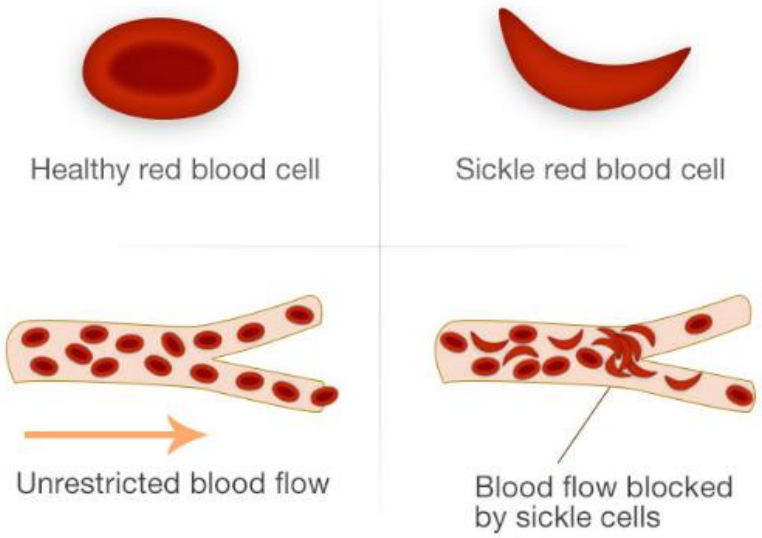
Sickling process is initially reversible, but with repeated sickling, cells eventually lose their membrane flexibility and become irreversibly sickled.

the normal adult red cell contains 96% HbA ($\alpha_2\beta_2$), 3% HbA2 ($\alpha_2\delta_2$), and 1% fetal Hb (HbF, $\alpha_2\gamma_2$)

SCA is typically manifested **after 6 months** when HbF levels fall and HbS increases .

Note that : because hemoglobin S has reduced oxygen affinity, oxygen delivery to tissues is enhanced, and patients may remain relatively asymptomatic despite anemia, except during crises or complications.

The sickling of red cells has two major pathologic consequences: chronic moderately severe **hemolytic anemia**, produced by red cell membrane damage, and **vascular obstructions**, which result in ischemic tissue damage and pain crises



Clinical features and complications

-Sickle cell disease is characterized by chronic hemolytic anemia and recurrent vaso-occlusive episodes that lead to intermittent severe pain and multiorgan injury.

-Homozygous sickle cell disease usually is asymptomatic until 6 months of age when the shift from HbF to HbS is complete.

-Younger patients usually have a relatively good health between crises, while older patients develop chronic morbidity from cumulative organs damage.

-Anaemia is usually moderate to severe (Hb 6–8 g/dL) with marked reticulocytosis (10–20%), but is often well tolerated due to cardiac compensation and the reduced oxygen affinity of HbS.

-The earliest presentation is frequently acute **dactylitis** (hand–foot syndrome) caused by vaso-occlusive necrosis of the small bones of the hands and feet, producing painful, swollen digits of varying length; with increasing age, the long bones are more commonly involved.

-Patients are prone to frequent infections due to splenic dysfunction results from repeated splenic vaso-occlusion by sickled red cells causes recurrent infarction,

progressive fibrosis, and eventual splenic atrophy (spleen is enlarged initially but autospleenectomy occurs with progression of age)

-Over time, multiple complications may arise, such as acute chest syndrome, stroke, chronic leg ulcers, vision problems, gallstones from bilirubin overload, and organ damage affecting the kidneys, lungs, and other systems.

-Acute chest syndrome, the second most frequent acute sickle cell–related event. Is a pneumonia-like illness characterized by chest pain, fever, cough, hypoxia, and a

-new pulmonary infiltrate on chest imaging.caused by infection, fat embolism from necrotic bone marrow in a vaso-occlusive crisis, or pulmonary infarction caused by sequestration of sickle cells

-Occlusion of the renal microvasculature leads to medullary ischemia and renal papillary necrosis (presents with hematuria, flank pain, and occasionally the passage of sloughed renal papillae in the urine.)

-SCA can be complicated by **moyamoya syndrome** , a progressive narrowing of brain arteries with a fragile collateral network and increased stroke risk. appear as “puff of smoke” on angiography.

-Recurrent vaso-occlusion of bone blood vessels lead to **avascular necrosis** of bones most commonly affecting the femoral and humeral heads (combination of bone infarction and functional asplenia, patients with sickle cell disease are at increased risk of osteomyelitis , particularly by Salmonella.

-Vaso-occlusion of the penile venous outflow cause **priapism** which is a painful, prolonged penile erection

-Growth and pubertal development may be delayed.

-Aplastic crisis with parvovirus B19 infection

"puff of smoke" appearance

Laboratory findings :

Hb 6–8g/dL

reticulocytosis

normal MCV (if MCV low, consider Fe deficiency or thalassaemia)

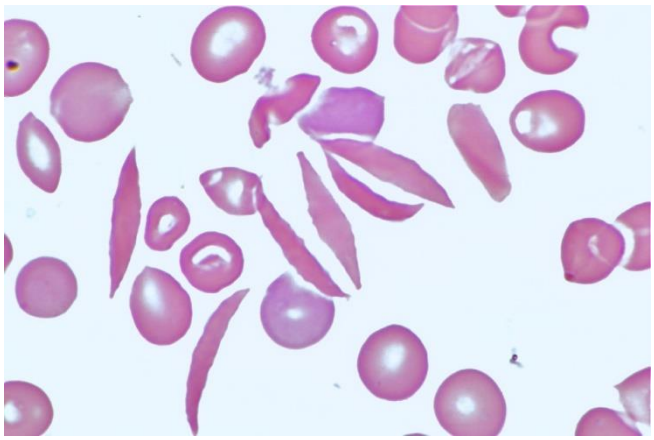
Sickle cells and **target cells** in the blood film

Howell-Jolly bodies

sickle solubility test (dithionate and Na2HPO4) will be positive if >20% HbS

Special investigations

- Hemoglobin electrophoresis
- Genetic / molecular studies



Management :

Management includes treatment of acute crises, prevention of infection, disease-modifying therapy with hydroxyurea, supportive care, and stem cell transplantation in selected cases.

Pain crisis: keep the patient hydrated and warm + analgesia ± O2

If there is fever start empiric broad-spectrum antibiotics + blood culture

Acute chest syndrome: O2 + antibiotics + analgesia ± exchange transfusion

Prevention of infection: Vaccinations + penicillin prophylaxis

Chronic management: Hydroxyurea + folic acid

(Hydroxyurea increase HbF concentrations , neutropenia is a frequent side effect so careful monitoring of blood count in essential)

Lifelong antimalarial prophylaxis is indicated in sickle cell disease (sickle cell trait confers partial protection against malaria , but sickle cell disease more susceptible to malaria)

There is other hemoglobin variants such as HBC , HBSC and HBE are beyond the scope of this review.

Thalassemia

Thalassemias are inherited disorders of hemoglobin synthesis characterized by reduced or absent production of one or more globin chains .

Decreased synthesis of one globin chain causes hemoglobin deficiency and red cell damage due to precipitation of excess unpaired normal globin chains.

HbA ($\alpha_2\beta_2$),HbA_2 ($\alpha_2\delta_2$) and HbF ($\alpha_2\gamma_2$)are the normal types of hemoglobin .

adult hemoglobin, or HbA, is a tetramer composed of two α chains and two β chains. In thalassemia, there is a quantitative defect in α- or β-globin chains

The mutations that cause thalassemia are particularly common in Mediterranean, African, and Asian regions in which malaria is endemic (hypothesized to be protective against malaria)

β-Thalassemia :

There are two copies of β-globin gene (one on each chromosome 11) .The defects in β-Thalassemia are mainly **point mutations**

If one copy is defective and produces no β-globin, that allele is termed β^0 (beta-zero), meaning no β-globin is made from that gene. If the mutation allows some β-globin to be made, it is called β^+ (beta-plus), meaning reduced (not absent) β-globin production.

The combination of affected genes determines the severity of β-thalassemia (i.e β-Thalassemia major, intermedia or minor)

Decreased or absent β-globin chain synthesis leads to excess unpaired α-globin chains. These α-chains precipitate in erythroid precursors and red cells, causing ineffective erythropoiesis and extravascular hemolysis

In the carrier (heterozygous) state, excess α chains combine with δ and result in modestly increased quantities of HbA2, which is used to screen for β-thalassaemia carrier status.

Heterozygous β-thalassaemia carriers exhibit asymptomatic microcytosis with or without mild anemia

β-thalassemia minor/trait

Asymptomatic , with mild or absent anemia

Blood film shows slight microcytosis and hypochromia (must be distinguished from iron deficiency by iron studies) . Also few target and tear drop cells

electrophoresis shows increased HbA2 (>3.5%)

β-thalassaemia intermedia :

Currently known as non-transfusion-dependent thalassaemia

occurs in patients in whom the pathological effects of excess α-globin chains are reduced(co-inheritance of α-thalassaemia or hereditary persistence of fetal Hb) , leading to a milder imbalance of globin synthesis and less severe ineffective erythropoiesis and hemolysis.

may also arise from the inheritance of a heterozygous β+mutation with an excess of α-chain genes (e.g extra α gene) . Normally heterozygous β+mutation is mild but the extra α-globin genes worsen β-thalassemia by increasing α/β globin imbalance.

Splenomegaly, bony expansion, and complications of Fe overload (even in the absence of regular blood transfusions due to increased intestinal iron absorption caused by ineffective erythropoiesis and hepcidin suppression)

β-thalassaemia major:

Currently known as transfusion-dependent thalassaemia

occurs in patients with homozygous or compound heterozygous β-thalassemia

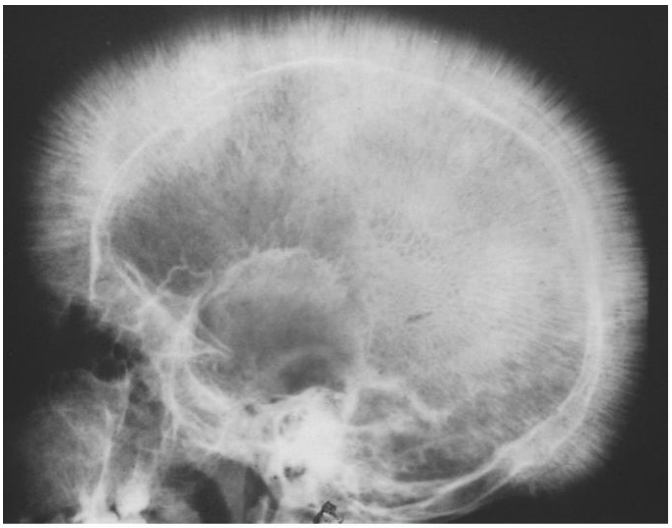
Most affected children present within the first year of life with :

failure to thrive and recurrent bacterial infections.

Severe anemia from 3 to 6 months, when the switch from γ- to β-chain production should normally occur

Extramedullary hematopoiesis that leads to hepatosplenomegaly and bone expansion, giving rise to the classical thalassaemic facies (Chipmunk face)

A “hair-on-end” appearance on skull X-ray is a characteristic finding in β-thalassemia major , reflecting marked bone marrow expansion due to ineffective erythropoiesis.

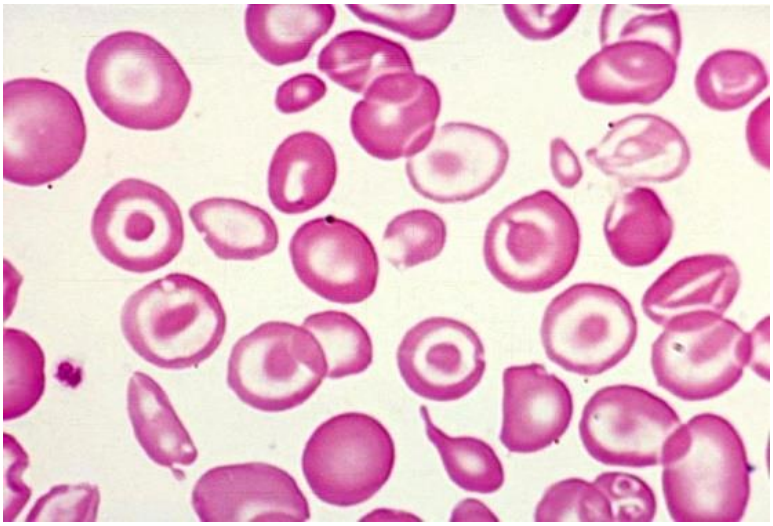


“hair-on-end” appearance on skull X-ray

There is a severe microcytic hypochromic anemia

Blood film shows many nucleated RBCs, tear drop and target cells

Electrophoresis shows absent HbA; increased HbF and HbA2



General management:

Refer to specialist centre

folic acid supplements

Splenectomy (weight pros and cons)

Management of iron overload

Bone marrow transplant (Considered in selected patients with suitable donors).

G6PD deficiency

Glucose-6-phosphate dehydrogenase deficiency is the most common enzyme deficiency worldwide and is inherited as an X-linked genetic defect.

Approximately 400 million people carry a mutated gene for glucose-6-phosphate dehydrogenase, although the majority are asymptomatic

G6PD is the first enzyme in pentose phosphate pathway (PPP) which is the main source of NADPH+H in the body
Although the enzyme deficiency is present in all tissues, only mature erythrocytes are seriously affected because they have no alternative routes for NADPH+H synthesis, and they cannot compensate for low enzyme activity by synthesizing more enzyme .

Adequate activity of the pentose phosphate pathway in erythrocytes is essential for maintaining reduced **glutathione**, an important antioxidant that protects red blood cells from oxidative damage. G6PD deficiency leads to reduced NADPH production and, consequently, depletion of reduced glutathione. As a result, erythrocytes lose their protection against oxidant stress, causing denaturation of hemoglobin and red cell membrane proteins.

Denatured proteins aggregate within the cell and appear as intracellular inclusions known as **Heinz bodies**. When affected erythrocytes pass through the spleen, splenic macrophages remove these inclusions, producing characteristic **"bite cells"** (degmacytes). The resulting membrane damage shortens red cell survival and leads to hemolysis, which may be intravascular or extravascular. Acute hemolytic episodes are precipitated by oxidant stress, such as infections, certain drugs (e.g., antimalarials, sulfonamides), or ingestion of fava beans. Clinically, this manifests as acute hemolytic anemia, jaundice, and dark-colored urine.

Clinical manifestations typically started 1-3 days after exposure

In exams, antimalarial exposure is a key diagnostic clue for G6PD deficiency , but in clinical practice the most common precipitating factor is infections, in fact patients with G6PD deficiency show improved malarial resistance profile . Ingestion of fava beans is also a famous precipitant

Management

- Avoid oxidative triggers
- supportive care during crises
- transfusion only if severe.

[G6PD levels may be falsely normal during acute hemolysis. RBCs with low G6PD enzymatic activity (older RBCs) are destroyed first, leaving younger RBCs with higher enzyme activity, causing falsely normal G6PD levels.]

Paroxysmal nocturnal hemoglobinuria :

PNH is an acquired chronic hemolytic anemia marked by persistent intravascular hemolysis with possible recurrent exacerbations , historically described as occurring at night (classically explained by mild respiratory acidosis during sleep that activate complement system which is the cause of hemolysis . But hemolysis is continuous rather than nocturnal)

Besides intravascular hemolysis, PNH is characterized by **thrombosis in unusual sites**, bone marrow failure, renal dysfunction, smooth muscle dystonia due to nitric oxide depletion, and iron deficiency.

This condition stems from the clonal expression of hematopoietic stem cells that have mutations in the **X-linked** gene **PIG-A** ,a gene required for the synthesis of phosphatidylinositol glycan (PIG), which serves as a **membrane anchor** for many proteins , including the complement regulatory proteins **CD55** (decay-accelerating factor) and **CD59** (membrane inhibitor of reactive lysis).

The pathogenic mutations in PNH occur in an early hematopoietic progenitor that is capable of giving rise to red cells, leukocytes, and platelets.

Clinical features

-The major clinical features are **intravascular hemolysis**, **venous thrombosis**, and **haemoglobinuria**.

-Hemolysis may be precipitated by infection, surgery, or iron therapy.

-Characteristically, the urine passed at night or on waking in the morning is dark . However , this is likely due to overnight accumulation of urine, making haemoglobinuria more apparent in the morning.

-In sever cases hemoglobinuria may be continuous, with all urine samples appearing dark.

-The most feared complication of PNH is **thrombosis** which often occurs within abdominal vessels such as the **portal vein** and the **hepatic vein**

-The cause of the increased predisposition to thrombosis is not known but may be:

- Complement-mediated activation of platelets deficient in CD55and CD59
- Hemolysis releases Hb in the plasma and lowers plasma nitric oxide.

Investigations

Evidence of intravascular hemolysis

Flow-cytometric analysis of RBCs with labeled anti-CD55 and antiCD59.

Bone marrow is sometimes hypoplastic

Management:

-Supportive

-Eculizimab, an antibody that binds C5 and inhibits the assembly of the C5b–C9 membrane attack complex, greatly lessens the incidence of thrombosis as well as the degree of intravascular hemolysis (Eculizimab has no effect on early stages of complement fixation, and treated patients continue to have varying degrees of extravascular hemolysis because of the deposition of C3b on red cell surfaces) . The drug is administered intravenously every 7 days for the first 5 weeks and then fortnightly (once every two weeks) .

Note that: The most serious risk of terminal complement blockade is infection with Neisseria meningitidis; thus, vaccination against N. meningitidis is recommended 2 weeks before commencing treatment

Extrinsic hemolytic anemias :

Hemolysis due to factors outside the red blood cell (RBC is structurally normal).

Causes :

Antibody-mediated

Isohemagglutinins: transfusion reactions, immune hydrops (Rh disease of the newborn)

Autoantibodies (AIHA) : idiopathic (primary), drug-associated, infection associated, malignancy associated, systemic lupus erythematosus

Mechanical trauma to red cells

- Microangiopathic hemolytic anemias: TTP , DIC , HUS
- March hemoglobinuria **:** damage to RBCs in the feet, associated with prolonged marching or running
- Damaged artificial heart valves

Infections: malaria

Splenic sequestration

Autoimmune hemolytic anemias (AIHAs)

Autoimmune hemolytic anaemias (AIHAs) are acquired disorders resulting from increased RBC destruction caused by RBC autoantibodies

These anaemias are characterized by the presence of a positive direct antiglobulin (**Coombs**') test result, which detects evidence of the presence of autoantibody (immunoglobulin [Ig] G, or complement) on the surface of the patient's RBCs (remember that indirect coombs' detects free antibodies in serum, mainly for pre-transfusion compatibility testing and antenatal antibody screening , and it has no essential diagnostic role in autoimmune hemolytic anemia) .

Depending on the optimal temperature at which the autoantibodies react with red blood cells , AIHAs are classified into two types :

- **Warm AIHA** : Antibodies react best at 37 °C with extravascular hemolysis and IgG immunoglobulin
- **Cold AIHA** : Antibodies react best at < 30 °C with extravascular hemolysis and IgM antibodies (hemagglutinin AIHA) or less commonly with intravascular hemolyisis and IgG immunoglobulin (hemolysin AIHA)
- Note that 5 % of patients have a mixed type

Warm AIHA (IgG-mediated):

- The most common type
- most frequent in middle-aged females

Etiology:

-Idiopathic

-Secondary : lymphoproliferative disorders , autoimmune disorders (e.g SLE) , drug-mediated (particularly α-methyldopa, penicillin and quinidine)

-The most common underlying cause is a lymphoproliferative disorder

Note that in secondary causes several distinct immunopathogenic mechanisms are involved, including immune dysregulation and alteration of red cell antigens) .

Pathophysiology

IgG autoantibodies bind to red cells

IgG autoantibodies do not usually activate the complement system causing intravascular lysis ; instead, they opsonize red blood cells and promote phagocytosis by splenic macrophages causing extravascular hemolysis.

Some IgG-coated erythrocytes are incompletely phagocytosed by splenic macrophages, leading to partial removal of the red cell membrane and spherocyte formation (acquired spherocytosis) .

Clinical features

Clinical severity is variable, but most patients have chronic mild anemia and moderate **splenomegaly** and require no treatment.

Signs and symptoms of the underlying cause (e.g arthralgia and rash in SLE)
Note that : The hemoglobin level may fall to as low as 4 g/dL within days, together with jaundice and splenomegaly; this raises suspicion of WAIHAs

Investigations

Evidence of HA

Spherocytosis

Positive coombs' test

Thrombocytopenia (Some patients may also have associated autoimmune thrombocytopenia (less commonly neutropenia may involved) as a part of Evans syndrome) .

Abdominal computed tomography (CT) should be carried out to detect abdominal lymphoma

Management:

- 1st line is corticosteroids prednisolone 1 mg/kg/day
- Rituximab (anti-CD20) 375 mg/m^2 weekly × 4 weeks as 2nd line if no response to corticosteroids
- If both corticosteroids and Rituximab fail consider spleenectomy

Cold AIHAs :

Usually caused by low-affinity **IgM** antibodies (or rarely IgG) that bind to red cell membranes at temperatures below 30 °C, such as in the distal parts of the body (ears, hands, and toes) during cold exposure.

Generally when we say cold AIHA , we mean the IgM-mediated type.

Cold hemagglutinin disease (IgM mediated):

Antibodies against **RBCs I antigen**

IgM antibodies bind red cells at low temperatures in peripheral parts of the body and fix complement , however these temperatures the complement cascade is usually not completed (As a result, erythrocytes become coated mainly with C3b without being hemolyzed intravascularly).

When these cells return to the warmer central circulation, IgM dissociates but the C3b coating persists, and because C3b acts as an opsonin, the erythrocytes are phagocytized by macrophages, predominantly in the **liver** and to a lesser extent in the spleen, resulting in extravascular hemolysis.

After exposure to cold, the patient develops an acrocyanosis similar to Raynaud's syndrome as a result of RBC autoagglutination.

Etiology

- Idiopathic/primary
- Secondary : triggered by infections (particularly **Mycoplasma pneumoniae and** Epstein-Barr virus) or underlying lymphoproliferative disorders

Management

Treat the underlying cause if possible

Avoid cold exposure

Steroids, alkylating agents (chemotherapy), and spleenectomy are usually ineffective

Rituximab may be beneficial

sutimlimab, a humanized monoclonal antibody selectively targeting the C1s protein, has been reported to produce rapid responses halting hemolysis

Paroxysmal cold hemoglobinuria (IgG-mediated):

rare condition associated with common childhood infections such as measles, mumps, and chickenpox, and in adults it has been classically associated with tertiary syphilis.

Donath–Landsteiner antibodies , a biphasic antibodies (binds RBCs at cold and activate complement-mediated lysis at warm) directed against RBCs **P antigen**

Unlike hemagglutinin disease , the complement cascade is completed after warming and predominantly intravascular hemolysis is occurs leading to hemoglobinuria .

Hemolysis is self-limiting, but RBC transfusions may be necessary.

POLYCYTHAEMIA

Polycythemia (or erythrocytosis) is defined as an increase in Hb or hematocrit (Hct). Hct is a more reliable indicator of polycythemia than Hb.

It can be :

-Relative polycythemia (Gaisböck's syndrome): Caused by reduced plasma volume with a normal red cell mass (hemoconcentration) .

-Absolute polycythemia :

- **Primary** : intrinsic bone marrow disorders (see polycythemia vera later)

- **Secondary**: caused by increased erythropoietin (EPO) production secondarily to the diseases such as chronic conditions with low oxygen levels or reduced renal perfusion, Chuvash polycythemia (defective oxygen-sensing EPO production pathway) or rarely EPO secreting tumor

Chapter 3 : White blood cells disorders an overview

Introduction

WBC disorders, similar to RBC disorders, can be broadly classified into deficiencies (e.g. neutropenia, lymphopenia) and, less commonly but more seriously ,neoplastic conditions (e.g. leukemias and lymphomas).

This section focuses on neoplastic hematological disorders, with emphasis on high-yield exam points.

Leukemia is a malignant neoplastic disorder of the **bone marrow** characterized by uncontrolled proliferation of abnormal leukocytes, which **spill over into the peripheral blood**. Leukemia is basically divided into acute and chronic types, each of which may be of myeloid or lymphoid origin.

On other hand, lymphoma is a malignant neoplastic disorder of the **lymphatic system** characterized by clonal proliferation of lymphocytes, typically presenting as **solid tumors** in **lymph nodes** or other lymphoid tissues. According to the presence or absence of **Reed–Sternberg** (**RS**) cells, lymphomas are divided into **Hodgkin** and **non-Hodgkin** lymphomas, respectively.

The distinction between leukemia and lymphoma is based on the **primary site of disease** (blood and bone marrow in leukemia , lymphoid tissues in lymphoma) , not the cell type.

leukemia and lymphoma may arise from the same cell type (e.g B-cell malignancies may present as leukemia (CLL) when there is predominant blood and bone marrow involvement , or as a lymphoma (SLL) when lymph nodes are predominantly involved.)

Some leukemias may involve lymph nodes and, in rare cases, transform into aggressive lymphomas (**Richter transformation**)

Some lymphomas may enter a leukemic phase with circulating malignant cells in the peripheral blood.

Warrant : Although cancer pathogenesis is a complex multistep process, this chapter focuses mainly on the important genetic associations in rather than detailed pathogenetic mechanisms.

Leukemias

In **acute leukemias**, there is rapid onset of symptoms, and the malignant cells are immature precursor cells (blasts). Classified into Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) .

While in **chronic leukemias**, the disease has an insidious onset with slow progression, and the malignant cells are more mature and differentiated . Classified into Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML)

Note that (Aleukemic leukemia is leukemia without the expected increase in white blood cells in the circulation)

Acute leukemias

Neoplastic proliferations of immature **precursor cells** (blasts) that proliferate in the bone marrow and subsequently spill into the peripheral blood and other tissues, leading to bone marrow failure and systemic manifestations.

Acute leukemias are defined by the presence of **≥20% blasts** in the bone marrow.

Myeloblasts and lymphoblasts often cannot be definitively differentiated by routine light microscopy alone so the differentiation requires special markers (e.g **TdT** which is a classical marker for lymphoblasts, and **myeloperoxidase** which is a classical marker for myeloblasts)

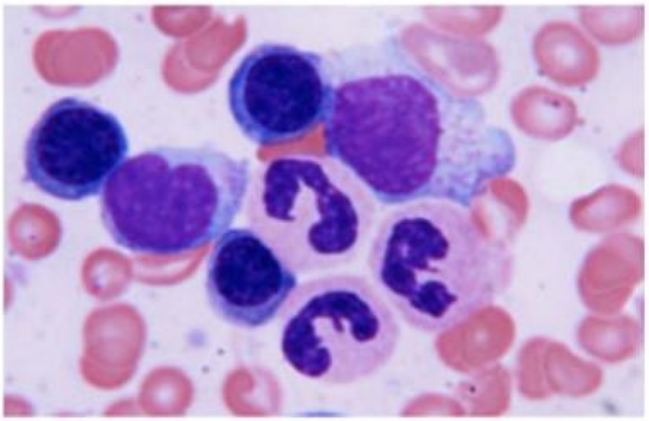
Most patients with acute leukaemia, regardless of subtype, present with one or more of the following:

Cytopaenia due to inadequate haemopoiesis secondary to infiltration of the bone marrow by leukaemia

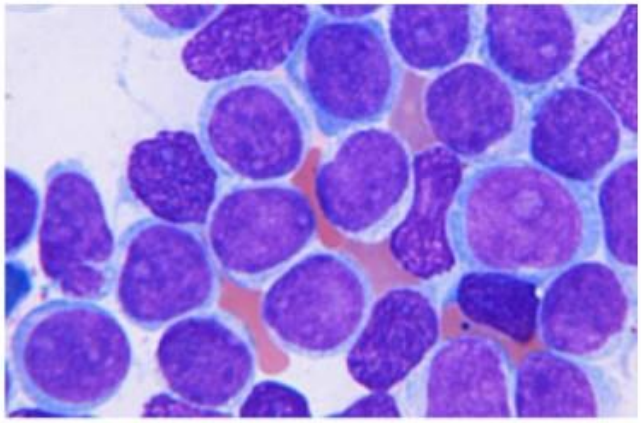
Symptoms caused by tissue infiltration by leukaemic cells (e.g bone pain , gum hyperplasia, hepatosplenomegaly, testicular enlargement, meningeal infiltration)

Clinical consequences of a high WCC in the circulation (e.g tumor lysis syndrome, hyperviscosity syndrome, leukostasis)

Symptoms caused by substance release from tumor cells (e.g fever , night sweat, weight loss , DIC)



Normal bone marrow



Bone marrow with acute leukaemia

Acute Lymphoblastic Leukemia (ALL) :

Is a malignant proliferation of **Lymphoblasts** , and it the most common cancer and a leading cause of cancer deaths in children

TdT (terminal deoxynucleotidyl transferase) is a DNA polymerase enzyme expressed in immature lymphoid precursor cells and is a hallmark marker of lymphoblasts. So TdT positivity is a characteristic feature of ALL.

ALL can be subclassified to B-ALL and T-ALL

B-ALL (85%) :

Typically presented in **childhood** (peaks in incidence at about the age of 3). And it is associated with **Down syndrome**, particularly after the age of 5 years

CD10 , CD19, CD20 are classical markers seen in B-ALL

CNS and **testicular infiltration** are common in B-ALL and they are sanctuary sites where leukemic cells are protected from systemic chemotherapy because of physiological barriers .

Generally B-ALLs has loss-of-function mutations in genes that are required for B cell differentiation

Genetic association:

hyperdiploidy (more than 50 chromosomes/cell) and (12;21) translocation in childhood and generally they are good prognosis

Philadelphia chromosome which is abnormal chromosome 22 formed by t(9;22) producing the BCR-ABL fusion gene and **associated with poor prognosis in adults** B-ALL.

(Philadelphia chromosome typically associated with CML and will be discussed later)

MLL (Mixed Lineage Leukemia) gene associated with aggressive and poor prognostic disease in infants

T-ALL (15%) :

less common form and tend to present in **adolescent** males as **thymic** "lymphomas."

cytoplasmic CD3 with early T-cell markers (**CD7**, CD2, CD5) are classical markers seen in PreT-ALL

[Note that because preT-ALL usually presented as lymphoma the disease in this situation called Acute Lymphoblastic Lymphoma and it is represent about 40% of childhood lymphomas].

Typically presents with an **anterior mediastinal mass**, which can cause symptoms due to compression of surrounding structures such as cough, shortness of breath, stridor, chest pain, and superior vena cava (SVC) syndrome

Management of ALL

The overall strategy is to achieve **remission** with induction chemotherapy followed by **consolidation** ± allogeneic **stem cell transplantation** in high-risk patients.

Treatment is with cycles of **chemotherapy**, and requires urgent transfer to a specialist center.

Intrathecal chemotherapy and, if needed local testicular irradiation are used to prevent relapse.

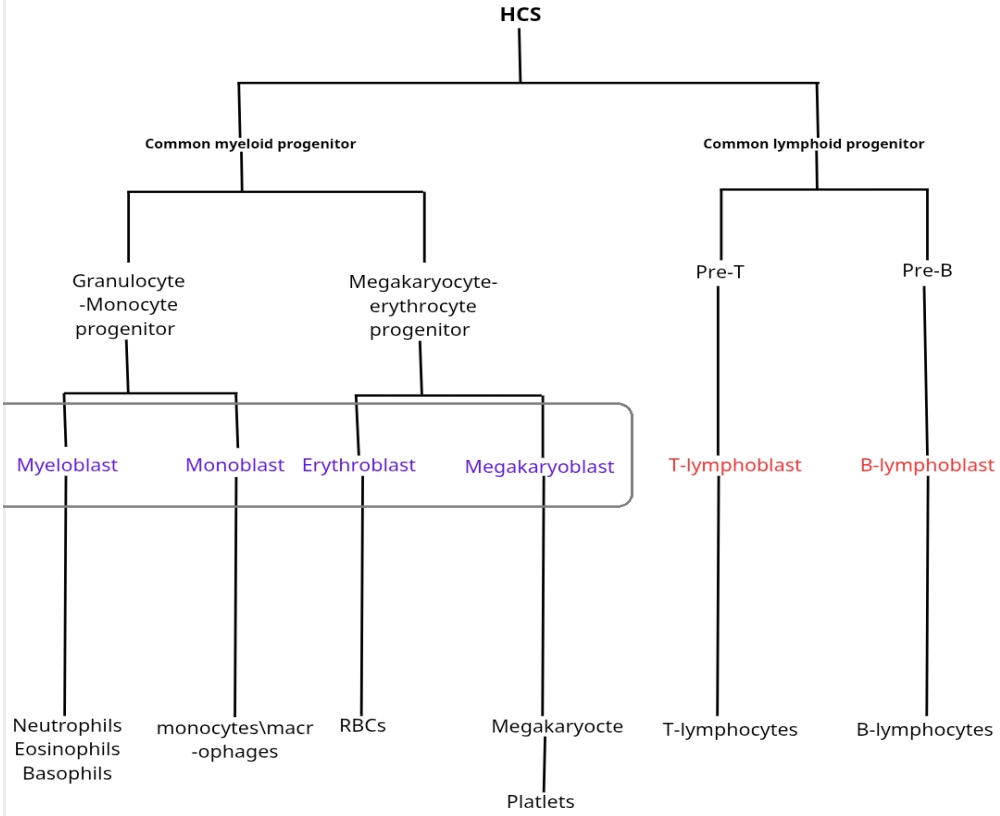
Treatment of t(9;22)-positive patients with **BCR-ABL kinase inhibitors** (e.g **Imatinib**) in combination with conventional chemotherapy is highly effective and has improved the outcome for this subtype of B-ALL in both children and adults

Supportive care

{With aggressive chemotherapy, about 95% of children with ALL obtain a remission, and 75–85% are cured.}

Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is a neoplasm of immature precursor myeloid cells (**myeloblasts** and their **equivalents**), which include granulocyte, monocyte, erythroid, and megakaryocytic precursors, which accumulate in the bone marrow and blood and lead to bone marrow failure.

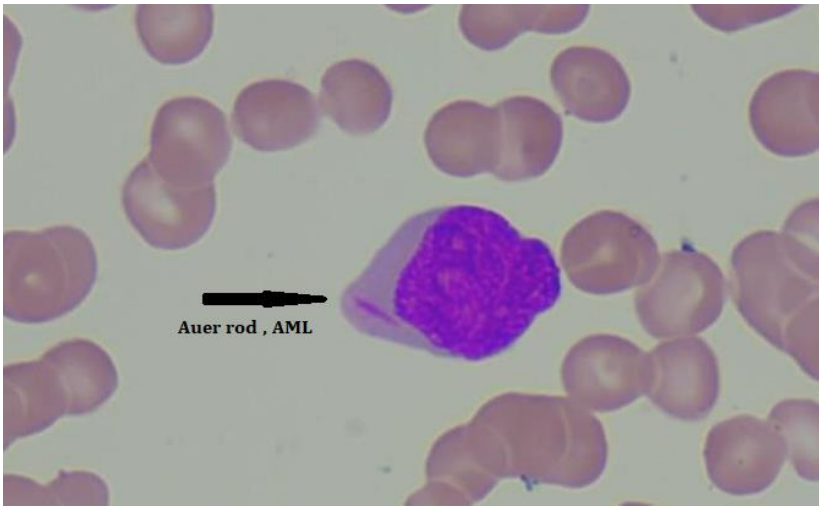


(**Acute leukemia in adults most likely=AML**)

Acute myeloid leukemia comprises a heterogeneous group of neoplasms with multiple classification schemes (e.g FAB, WHO) , however detailed discussion of these classifications is beyond the scope of this book.

Myeloperoxidase (MPO) is a specific marker for myeloid lineage and is useful in distinguishing AML from ALL; however, it is not positive in all AML subtypes

Auer rods are needle-shaped cytoplasmic inclusions formed by fusion of primary granules (containing MPO) seen in AML (not all subtypes) , and it is associated with hypercoagulability and DIC



The most frequently reported AML subtypes include **M2**, M4, and M1 (according to FAB classification, from M1-M7)

Acute-Promyelocytic Leukemia (M3) is a less frequent subtype (5-10%) but is clinically important because :

- It is a medical emergency ,uniquely associated with a severe, life-threatening **coagulopathy** associated with multiple Auer rods in a "**faggot cells**"
- Pathognomonic genetic basis involving the t(15;17) translocation that produces the PML-RARA fusion gene , which creates an **abnormal retinoic acid receptor** (Vit A receptor) .
- Highly curable with targeted therapy (**all-trans retinoic acid** + arsenic trioxide)

Acute Monoblastic Leukemia (M5) , relatively more common in children ,and characteristically associated with **gingival (gum) infiltration .**

Acute Megakaryoblastic Leukemia (M7) , a rare subtype and it is usually associated with down syndrome before age of 5 years .

Note that: Chloroma (also called myeloid sarcoma or granulocytic sarcoma) is a solid mass of leukemic myeloid cells outside the bone marrow. And up to approximately 10–30% of African pediatric AML may present with chloroma.

Management

Includes induction chemotherapy to achieve remission, consolidation therapy to prevent relapse (with possible stem cell transplant for high-risk patients), targeted therapy for specific genetic subtypes, and supportive care.

Where specialist care is not available, hydroxycarbamide (adult dose 1–2 g/day) may temporarily reduce the white blood cell count and improve symptoms.

Poor prognosis is associated with age >55yrs

{ The term myelodysplastic syndrome (MDS) refers to a group of clonal stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis and a high risk of transformation to AML ,Historically, myelodysplastic syndromes were referred to as pre-leukemic syndromes, because a proportion of cases progress to acute myeloid leukemia (AML) }

Chronic leukemias

Neoplastic proliferation of **relatively mature, well-differentiated** but functionally abnormal leukocytes, which accumulate in the bone marrow, peripheral blood, and other tissues

The disease typically follows an indolent course, with preserved cell maturation and **<20% blasts** in the bone marrow, and is **often detected incidentally** during routine blood examination.

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a neoplasm of **mature B lymphocytes** characterized by the progressive accumulation of **functionally incompetent lymphocytes** in the peripheral blood, bone marrow, spleen, and lymph nodes due to defects in apoptosis rather than increased proliferation.

It is **the most common type of leukaemia**, increasing in incidence with age; the median age of presentation is around 70 years , and males affected more than females.

Most patients are diagnosed incidentally on routine blood tests (blood tests showing lymphocytosis, typically with a total **lymphocyte count> 5000 cells/µL**)

And the diagnosis is confirmed by flow cytometry demonstrating a monoclonal B-cell population with the characteristic **co-expression of CD20 and unusual CD5** (remember that CD5 is primarily a T-cell marker, which is aberrantly expressed on malignant B cells in CLL. Coexistence of it with normal CD20 is highly suggestive for CLL)

Smudge cells (or **basket cells)**, a damaged, fragile lymphocytes that rupture during slide preparation is a characteristic morphologic finding in CLL

Small Lymphocytic Lymphoma (**SLL**) is the same disease as CLL but with predominant nodal involvement and insufficient lymphocytosis to meet threshold of CLL . So the disease is usually termed **CLL/SLL**

CLL and SLL are different clinical presentations of the same disease , having the same malignant cells , immunophenotype and treatment.

CLL is strongly associated with **immune dysregulation**, which affects both humoral and cellular immunity but particularly impairs normal B-cell function .

Through unclear mechanisms, the accumulation of CLL/SLL cells suppresses normal B-cell function, often resulting in progressive **hypogammaglobulinemia** with impaired antibody production. Paradoxically, the same immune dysregulation predisposes to autoimmune phenomena, and approximately 7–15 % of patients develop autoantibodies against their own red cells or platelets, resulting in **autoimmune hemolytic anemia** (AIHA) and immune thrombocytopenia, respectively.

Genetic association :

the most common of which are trisomy 12 and deletions involving portions of chromosomes 11, 13, and 17.

Deletion of 17p, which usually involves the **TP53 gene** (the guardian of the genome), is associated with the **worst prognosis** among these abnormalities

Clinical features :

Most patients are asymptomatic at presentation. If present, symptoms are non-specific

Common symptoms are:

Recurrent infections due to immune dysfunction

Anemia, caused by bone marrow infiltration or autoimmune hemolysis, often clinically apparent.

Painless lymphadenopathy, typically small-volume, easily palpable, and often present for a long period before diagnosis.

Splenomegaly-related symptoms, such as left upper quadrant discomfort or early satiety.

Constitutional symptoms, similar to B symptoms

Management

-Most patients with CLL/SLL are asymptomatic at diagnosis, and initial management is usually **observational** (watch and wait) because starting therapy early in asymptomatic patients does not improve overall survival compared with waiting until the disease shows progression or causes symptoms (early treatment in this setting does not prolong life and may expose patients to unnecessary side effects and complications) .

-Indications of treatment :

- Bone marrow failure.
- Massive or progressive splenomegaly or lymphadenopathy.
- Systemic symptoms: fever, night sweats, or weight loss.
- Progressive disease demonstrated by doubling of the lymphocyte count in less than 6 months.
  Presence of hemolysis or other immune-mediated cytopaenias that are poorly responsive to steroids.

-Targeted therapy:

BTK inhibitors: ibrutinib and acalabrutinib (approved 2014)

FCR (fludarabine + cyclophosphamide + rituximab)

BCL-2 inhibitors : venetoclax

-Supportive therapy (e.g steroids for AIHA)

{In rare situations, CLL/SLL can transform into a more aggressive diffuse large B-cell lymphoma (**Richter's transformation**) . This transformation is manifested by a rapid clinical deterioration often with rapidly enlarging lymph nodes, B symptoms (such as fever, night sweats, and weight loss), and other signs of aggressive lymphoma, and requires different, more aggressive therapy compared with standard CLL treatment.}

Chronic Myeloid Leukemia (CML)

Before discussing CML, it is important to highlight **myeloproliferative neoplasms** (MPNs).

CML is one of the recognized types of myeloproliferative neoplasms

Myeloproliferative neoplasms are a group of clonal hematopoietic stem-cell disorders characterized by **increased proliferation of one or more mature myeloid cell lineages** (i.e red blood cells, granulocytes, and platelets) . Commonly associated with acquired mutations that lead to constitutive activation of tyrosine kinases (e.g JAK-2 mutation, Philadelphia chromosome .

CML is a subtype characterized by predominantly increased granulocytic leukocytes

[Other types of MPNs including polycythemia vera, myelomonocytic leukaemia, thrombocythemia and myelofibrosis are not discussed here and will be discussed in other book soon]

Chronic myeloid leukemia (CML) is distinguished from other myeloproliferative neoplasms by the presence of the **Philadelphia chromosome**

Philadelphia chromosome is an abnormal, shortened chromosome 22 that results from a reciprocal translocation between chromosomes 9 and 22 , leading to the formation of the **BCR-ABL1 fusion gene**.

BCR-ABL1 fusion gene encodes a constitutively active tyrosine kinase that drives uncontrolled proliferation

Note that: Philadelphia chromosome may be seen in some cases of ALL; however, unlike CML, the presence of the Philadelphia chromosome is associated with more aggressive disease behavior and a poorer prognosis.

CML can transform to acute leukemias (to AML or less commonly ALL)

CML is almost exclusively a disease of adults, with presentation between 40 and 60 years of age

Clinical features:

Chronic phase : often mild or asymptomatic , WBC elevated ; good response to therapy.

CML is the most characteristic leukemia with very high WBC at diagnosis

Accelerated phase : increasing blasts and worsening symptoms; signs of disease progression.

Blast crisis: aggressive phase resembling acute leukemia with high blast counts and severe symptoms.

Note : Priapism, a painful and prolonged erection, is a rare complication of leukemia that is seen most commonly in patients with CML

Blood tests findings:

- Hb is low or normal
- WCC is high (usually >100 × 10^9/L) with predominant neutrophilia and a left-shifted granulocytic picture . The presence of increased **basophils** is a characteristic and important finding in CML, with both diagnostic and prognostic value
- platelet count can be low, normal, or high.

Management

Targeted therapy: **tyrosine kinase inhibitors** such as imatinib

Most patients diagnosed with chronic-phase CML have a normal life expectancy

Note that :

CML must be distinguished from a **leukemoid reaction** because the latter is a benign reactive leukocytosis, whereas CML is a malignant myeloproliferative neoplasm.

Key differentiators include **basophilia**, **low LAP** (leukocyte alkaline phosphatase) score, and the presence of the **Philadelphia chromosom**e in CML.

Lymphomas

As mentioned earlier, lymphomas are malignancies of the **lymphatic system** characterized by clonal proliferation of lymphocytes, typically presenting as **solid tumors in lymph nodes** or other lymphoid tissues.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are two sides of the same coin. They represent two clinical presentations of the same disease entity, reflecting different manifestations—one as leukemia and the other as lymphoma—of an identical underlying B-cell neoplasm. This example illustrates the blurred and delicate boundaries between leukemia and lymphoma.

(See introduction to deeply understand the concepts Leukemia and lymphoma)

Classically, lymphomas are first divided into two major categories ,**Hodgkin lymphoma** and **non-Hodgkin lymphomas** . Hodgkin lymphoma is defined by the presence of **Reed-Sternberg cells**, while non-Hodgkin lymphoma includes all other lymphoid malignancies without Reed-Sternberg cells.

Hodgkin's Vs Non-Hodgkin's

Feature	Hodgkin's	Non-Hodgkin's
Reed-Sternberg cells	absent	present
Spread pattern	Predictable, Contiguous, sequential nodal spread	Non-predictable, non-contiguous
Age distribution	Bimodal: young adults (20s) & older adults (>55)	More common in older adults
Extranodal involvement	uncommon	common

Clinical features

Clinical presenting features and symptoms can range wildly between the different types of lymphoma

Most patients present with **peripheral lymphadenopathy** or symptoms due to **involvement of deep lymph nodes**.

Approximately 20% of patients present with disease involving extranodal sites, such as the gastrointestinal tract, skin, or central nervous system

Only a small proportion of patients present with lymphoma-associated B symptoms, including weight loss, fever, and night sweats, despite their prominence in medical textbooks (Kumar and Clark's Clinical Medicine, 2022).

General management of lymphoma

Initial management of suspected lymphoma focuses on establishing an accurate diagnosis by excisional biopsy (or aspiration), appropriate pathological review, and MDT discussion ,while avoiding pre-biopsy steroids where possible.

The treatment strategy depends on the lymphoma subtype, stage of disease, and patient-related factors.

Non-Hodgkin's Lymphomas

NHLs are a heterogeneous group of lymphoid malignancies that arises from abnormal proliferation of lymphocytes (mostly B-cells, but also T-cells or NK-cells) . NHL has diverse subtypes ranging from indolent to aggressive behavior.

Unlike Hodgkin lymphoma, NHL lacks Reed-Sternberg cells and demonstrates non-contiguous spread

Typically presents with painless lymphadenopathy, often at multiple sites, and may involve extranodal organs such as the CNS, skin, gastrointestinal tract, or bone marrow.

[Extranodal involvement such as GI tract, skin and CNS involvement is almost always NHL]

Pre-T Acute Lymphoblastic lymphoma: discussed earlier

Small Lymphocytic Lymphoma: discussed earlier

Diffuse large B cell lymphomas (DLBCL)

Diffuse large B cell lymphoma is the most common type of lymphoma in adults, and the second most common lymphoma in childhood.

[DLBCL is the most common lymphoma overall , accounting approximately 30 % of all cases]

DLBCL can present in several ways. It may arise de novo (sporadically), or it may represent **histological transformation** from a pre-existing indolent B-cell lymphoma, most commonly follicular lymphoma and less commonly SLL/CLL (**Richter transformation**).

These tumors express the B cell antigen **CD20**

DLBCL is considered an AIDS-defining condition . In people with HIV, certain types of non-Hodgkin lymphomas , including DLBCL, Burkitt lymphoma, and primary central nervous system lymphoma are classified as AIDS-defining cancers. The development of one of these lymphomas in an HIV-positive individual fulfills criteria for the diagnosis of AIDS, reflecting advanced immunosuppression and high lymphoma risk in this setting.

Clinical features

-Patients typically present with a rapidly enlarging, often symptomatic (painful, mass effect, B symptoms) mass at one or several sites.

-Extranodal presentations are common. **The gastrointestinal tract is the most common extranodal site**, but tumors can appear in virtually any organ or tissue.

-involvement of the liver, spleen, and bone marrow is not common at diagnosis.

-Intra-abdominal disease , presents with bowel symptoms caused by compression or infiltration of the gastrointestinal (GI) tract (e.g epigastric/abdominal pain, GI bleeding, obstruction). If a patient has rapid weight loss , palpable mass , obstruction symptoms DLBCL should be considered

-Primary CNS lymphoma arises in the CNS and is usually DLBCL . It occurs both in immunocompetent and immunocompromised patients and typically presents with focal neurological deficits, symptoms of increased intracranial pressure (such as headache and nausea), cognitive or behavioral changes, and occasionally seizures.

Treatment

Rituximab , an anti-CD20 monoclonal antibody is combined with chemotherapy as the backbone of treatment for Diffuse Large B-Cell Lymphoma .

The standard first-line regimen for most patients is **R-CHOP** (rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone).

Follicular Lymphoma (FL)

the second most common lymphoma and accounts for approximately 20% of lymphomas worldwide

occurs in middle to late life (very rare in childhood)

Greater than 85% of follicular lymphomas have a characteristic t(14;18) translocation that fuses the BCL2 gene on chromosome 18 to the IgH locus on chromosome 14. This chromosomal rearrangement results in inappropriate overexpression of the BCL2 protein, which inhibits apoptosis.

Follicular lymphoma is usually an indolent (slow-growing) lymphoma, but it can transform into aggressive lymphoma (i.e DLBCL, This transformation is an ominous event, as tumors arising from this transformation is much less curable than de novo diffuse large B-cell lymphomas)

Follicular lymphoma must be distinguished from reactive lymphadenopathy (benign response to infection , histologically can mimic FL) . Follicular lymphoma shows a **monoclonal** proliferation of neoplastic B cells with **BCL2 overexpression** and effacement of normal nodal architecture, whereas reactive lymphoid hyperplasia is **polyclonal** with preserved architecture and **lacks BCL2 overexpression.**

These tumors express B cell markers such as **CD20** and the germinal center B cell markers **CD10** and **BCL6**

FL, usually manifests as painless, generalized lymphadenopathy. The bone marrow is involved at diagnosis in approximately 80% of cases.

cytotoxic drugs and rituximab (anti-CD20 antibody) is reserved for those with bulky (large lymphoma mass usually >10 cm), symptomatic disease.

Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma and is the most common form of non-Hodgkin lymphoma in children . And it is the most rapidly proliferating lymphoma.

In parts of sub-Saharan Africa and other malaria-endemic regions (historically described as the lymphoma belt) Burkitt lymphoma can account for up to 30–50 % of all childhood cancers, making it the most common childhood malignancy in these areas.

Burkitt lymphoma is driven by MYC activation due to t(8;14).

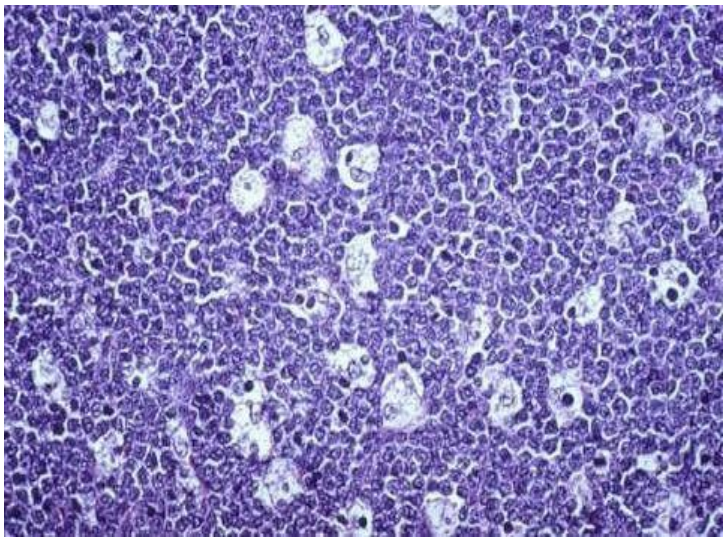
BL has three histopathologically identical subtypes :

- **Endemic EBV-related (African)** type , which typically presents in children with a large **jaw** or **facial tumor**
- **Sporadic** type, which more commonly presents with **abdominal masses**
- **immunodeficiency-associated** type seen in patients with HIV or other immunosuppression.

The hallmark histopathological feature of Burkitt lymphoma is the classic "**starry-sky**" appearance .

Burkitt lymphoma requires urgent, intensive chemo-immunotherapy with tumor lysis prophylaxis and mandatory CNS prophylaxis.

Endemic Burkitt lymphoma



Mantle cell lymphoma

Mantle cell lymphoma is composed of cells resembling the naive B cells found in the mantle zones of normal lymphoid follicles. Usually presents later in life and has a male-to-female ratio of 3 to 1

Like CLL/SLL, these cells express normal B-cell markers such as CD19 and **CD20** with unusual T-cell marker **CD5** , but they are typically **negative for CD23** which helps distinguish it from CLL/SLL

MCL typically presents with painless, generalized lymphadenopathy and often advanced stage at diagnosis.

B symptoms occur in about one-third of patients.

Bone marrow and GI tract are frequently involved, and circulating lymphoma cells may be present.

MCL can range from an indolent, slow-growing disease to an aggressive lymphoma, with most cases following an aggressive course. (indolent clinical course may be observed for years without treatment before therapy becomes necessary.)

MCL is characterized by a t(11; 14), translocation that leads to overexpression of **cyclin D1**, a protein that promotes cell cycle progression.

Mantle Cell Lymphoma International Prognostic Index (MIPI) is a special grading/prognostic system used for MCL to predict how the disease might behave and to guide the management plan.

MCL management is individualized: intensive therapy and stem cell transplantation for young fit patients, and less intensive therapy for older or unfit patients.

Extranodal marginal zone lymphoma (mucosa-associated lymphoid tissue lymphoma) :

It is an uncommon B-cell lymphoma associated with chronic inflammatory conditions (e.g H.pylori , Sjögren syndrome and Hashimoto thyroiditis).

Persistent inflammation can create acquired lymphoid aggregates in tissues that normally lack them, and ongoing immune stimulation in these aggregates can drive the development of extranodal marginal zone B-cell (MALT) lymphoma.

The **stomach is the most common** site of MALT lymphoma, often linked to H. pylori infection , the patient presents with symptoms of gastric ulceration or a mass, indigestion, or bleeding . Eradication of H. pylori with antibiotic therapy often leads to regression of the tumor cells ,because the lymphoma cells depend on inflammatory cytokines produced by H. pylori-specific T cells for survival.

Low-grade gastric MALT lymphoma is treated first with H. pylori eradication; if this fails, rituximab, chemotherapy, or radiotherapy are effective, with an excellent prognosis.

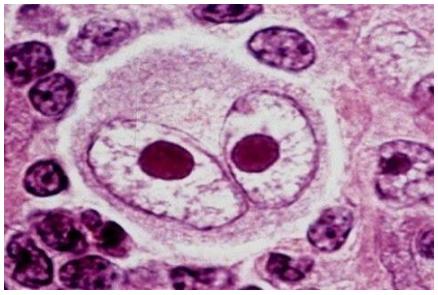
Lymphoplasmacytic Lymphoma : rare NHL associated with a monoclonal IgM paraprotein (Waldenström's macroglobulinemia)

Mycosis Fungoides (cutaneous T-cell lymphoma) : the most common cutaneous lymphoma, with an indolent course and initial skin-limited disease. Sézary syndrome is the leukemic variant of MF characterized by early blood involvement.

Hodgkin's lymphoma

Hodgkin lymphoma is characterized by the presence of Reed–Sternberg cells or their variants (lacunar cells and popcorn cells) within a characteristic inflammatory background. RS-like cells may occasionally be seen in non-Hodgkin lymphomas, but they lack the typical mixed inflammatory background seen in HL

Reed–Sternberg cells are large neoplastic cells with a characteristic "owl's eye" appearance . They are usually derived from germinal-center B lymphocytes, but they typically lose normal B-cell markers and express unusual CD30 (and often CD15). this immunophenotype is crucial not only for diagnosis but also for the use of novel targeted therapies, particularly **anti-CD30 agents**.



RS cells usually constitute only about 1–5% of the total tumor mass, with the majority of the lesion composed of reactive inflammatory cells recruited by cytokines released from RS cells.

The aetiology of HL is unknown .Positive antibody titres against EBV are found in 40%

HL typically presents with painless lymphadenopathy (most commonly cervical) , often spreading in a contiguous fashion from one lymph node group to the next. B symptoms are present in about one-third of patients with HL . pruritus is a common associated symptom that may occur independently of B symptoms.

According to the World Health Organization (WHO) classification, Hodgkin lymphoma (HL) is divided into two main categories , **classical Hodgkin lymphoma (cHL)** and **nodular lymphocyte-predominant Hodgkin lymphoma** (**NLPHL**).

Classical Hodgkin lymphoma is further subdivided into four histologic subtypes: **nodular sclerosis**, **mixed cellularity**, **lymphocyte-rich**, and **lymphocyte-depleted**.

Nodular sclerosis is the most common HL , and the only type with female predominance . Often presents with mediastinal mass and it has a good prognosis.

Special variants of RS cells namely **popcorn cells** and **lacunar cells** are found in specific subtypes. Popcorn cells are characteristic for NLPHL , and lacunar cells are found in nondualr sclerosis cHL .

Popcorn cells usually lack CD30 and express **CD20**

HL generally has a good prognosis with high long-term survival, especially in early stages; NLPHL has the best outlook, while lymphocyte-depleted subtype has the poorest.

Management

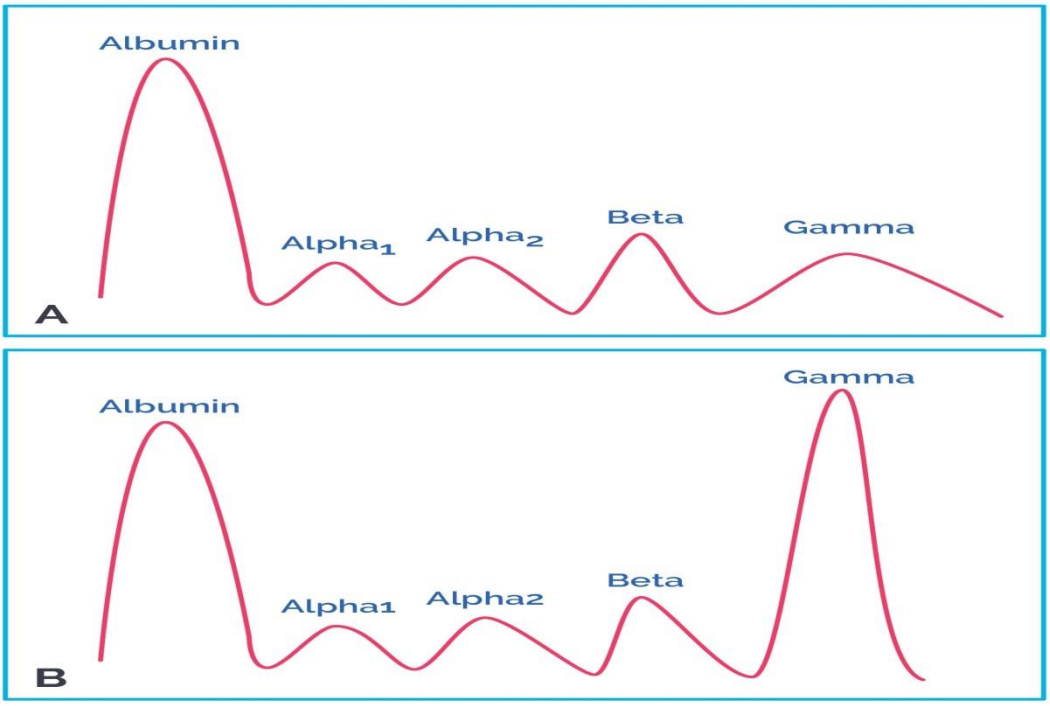
Hodgkin lymphoma is managed with curative chemotherapy (± radiotherapy), with more intensive or targeted therapy used in relapse.

There are multiple chemotherapy regimens used in the treatment of Hodgkin lymphoma, including ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) and AVD (Adriamycin, vinblastine, and dacarbazine) ,chosen based on disease stage and patient factors.

Multiple myeloma

Multiple myeloma (MM) is part of a group of conditions known as **plasma cell dyscrasias** (also called monoclonal gammopathies). These disorders are characterized by clonal proliferation of plasma cells that produce a monoclonal immunoglobulin (called **paraprotein** or **M protein**). Most common immunoglobulin is **IgG**.

M protein is usually detected by serum protein electrophoresis (SPEP) as a monoclonal "**M spike**" and may appear in urine as **Bence Jones proteins** (free light chain)



M spike in multiple myeloma (B), compare with normal serum protein electrophoresis (A)

Bence Jones proteinuria is classically seen in MM

IL-6 is a major cytokine that drives myeloma cell growth and survival, and myeloma cells are often considered IL-6 dependent. IL-6 has been studied as a therapeutic target in MM

In MM, RBCs classically show **rouleaux** formation (stacked like coins) on smear.

Clinical features

-Anemia : myeloma cells crowd out normal bone marrow cells

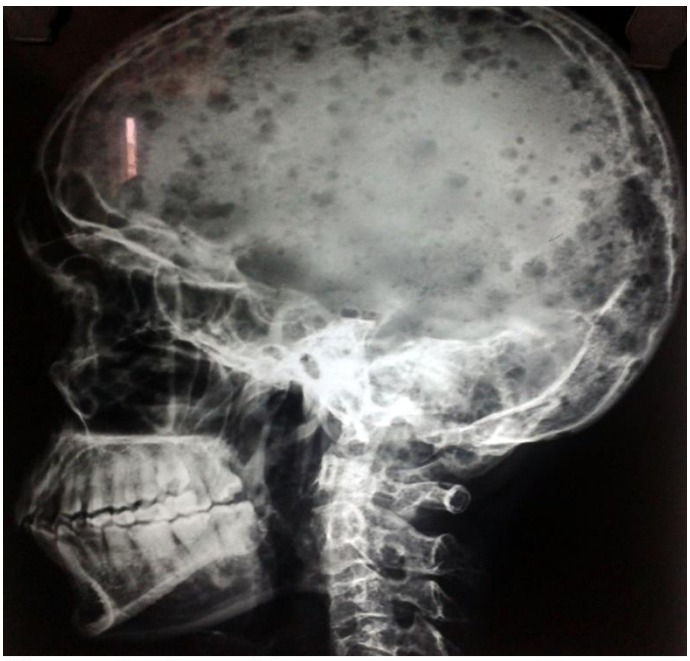
-Bone pain and other issues : myeloma cells cause increased bone destruction by stimulating osteoclasts and inhibiting osteoblasts , this results in characteristic lytic "**punched-out**" bone lesions on imaging . Vertebral collapse and loss of height may occur.

-Hypercalcemia : bone breakdown releases calcium into the blood.

-Renal dysfunction (affect 50%) due to :

- Light chain cast (myeloma kidney or light-chain cast nephropathy) . Free light chains bind with **Tamm-Horsfall** protein in the distal tubules, forming obstructive casts . These casts block the tubules, trigger inflammation, and lead to acute kidney injury or chronic tubular damage
- Free light chains are also directly toxic to renal tubular cells, especially the proximal tubules .
- Renal dysfunction also can be initiated by direct deposition of light chain in renal structures, leading to either light-chain deposition disease (LCDD) or AL amyloidosis.
- Other factors including infections and hypercalcemia are also contribute in renal damage

-Increased infection risk : myeloma cells suppress normal plasma cells and reduce production of normal antibodies. The most common infections are **pneumonia** and **pyelonephritis** .the most frequent pathogens are Streptococcus pneumoniae, Staphylococcus aureus, and Klebsiella pneumoniae in the lungs and Escherichia coli and other gram-negative organisms in the urinary tract .



"**punched-out**" lesions

Diagnostic criteria:
Bone marrow plasma cells > 10% or extramedullary plasmacytoma plus at least one of the following:

M-protein in the serum

M-protein in urine
Lytic bone lesions

Management:

Supportive : treat anemia, pain , renal failure, hypocalcemia, spinal cord compression , hyperviscosity if present .

Specific therapy : combination drug therapy , not curative but may prolong survival and reduce complications

Stem cell transplantation

(median survival of 3 years)

Other plasma cell dyscrasias including monoclonal gammopathy of undetermined significance (MGUS) , smoldering multiple myeloma, Waldenström macroglobulinemia, Heavy-chain diseases and AL amyloidosis are beyond the scope of this book .

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